EVIDENCE-BASED PRIORITY SETTING for health research

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EVIDENCE-BASED PRIORITY SETTING for health research
COLOFON

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<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Summary</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>Introduction</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>The mismatch between the health R&amp;D that is needed and the R&amp;D that is undertaken: an overview</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>Health research prioritization at WHO</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>A checklist for health research priority setting: nine common themes of good practice</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>Aid alignment for global health research: the role of HIROs</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>Mapping available health R&amp;D data: what’s there, what’s missing and what role for a Global Observatory</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>Use of data from registered clinical trials to identify gaps in health research and development</td>
<td>120</td>
</tr>
<tr>
<td>8</td>
<td>Finding better ways to fill gaps in pediatric health research</td>
<td>146</td>
</tr>
<tr>
<td>9</td>
<td>Pharmacokinetic research in children: an analysis of registered records of clinical trials</td>
<td>156</td>
</tr>
<tr>
<td>10</td>
<td>The quality of registration of clinical trials</td>
<td>178</td>
</tr>
<tr>
<td>11</td>
<td>The quality of registration of clinical trials: still a problem</td>
<td>198</td>
</tr>
<tr>
<td>12</td>
<td>Information on blinding in registered records of clinical trials</td>
<td>224</td>
</tr>
<tr>
<td>13</td>
<td>Discussion</td>
<td>232</td>
</tr>
<tr>
<td>DS</td>
<td>Dutch summary</td>
<td>Samenvatting</td>
</tr>
<tr>
<td>A</td>
<td>Acknowledgements</td>
<td>Dankwoord</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum vitae</td>
<td>List of publications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>268</td>
</tr>
</tbody>
</table>

Every year, approximately 240 billion US dollars are spent globally on health research and development (R&D). Over the past century, health research has led to the development of knowledge and products that have saved many lives. However, simultaneously, important areas of research have remained largely neglected. To date, one of the most pressing problems in global health is that there is a mismatch between the health R&D that is needed and the R&D that is undertaken.

This thesis shows that the lack of health R&D for populations in low-income countries is an important part of this mismatch. However, the mismatch is broader than this problem, and also affects high-income countries. This thesis makes clear, for example, that there are gaps in paediatric health research. Another example is the lack of research on new antibiotics. Moreover, both in low-income and in high-income countries, some health problems receive more attention, in terms of health R&D, than others.

There are several causes of this mismatch. These include the dependence of health R&D on market incentives in the for-profit private sector; the tension between national-level priorities and global-level priorities for health research; the influence of factors other than the need for health research on funding allocation decisions by public and philanthropic funders (such as the testimonials of advocacy groups); the lack of coordination by public and philanthropic funders on global priorities for health research; and the lack of appropriate processes for health research prioritization at the global level. This thesis focuses on the latter of these causes. It examines the processes underlying health research prioritization at the global level and makes suggestions for improvement.

PROBLEMS WITH GLOBAL-LEVEL HEALTH RESEARCH PRIORITIZATION

The goal of setting health research priorities is to identify research with the greatest potential public health benefit (such as decreased burden of disease or increased equity). There are several problems with the present processes for global-level health research prioritization. First, there is currently no system to comprehensively (for all health problems and all countries), systematically (using fair and legitimate methods), and periodically map what health R&D is most needed globally. Second, when research priorities are set, the processes that are used are often of sub-standard quality. Third, the information that needs to be collected as part of priority setting processes is often not available. Fourth, when research priorities are set, it is often not clear how they will be implemented.
DEVELOPING METHODS FOR HEALTH RESEARCH PRIORITY SETTING PROCESSES

This thesis contributes to the development of solutions to these problems. One contribution is the checklist for health research priority setting that is presented in the thesis. The checklist was developed through a review of health research priority setting exercises at the World Health Organization (WHO), a review of the literature on health research priority setting methods, and key stakeholder interviews. It helps researchers and policymakers to establish high-quality health research priority setting processes by describing nine common themes of good practice for such processes.

THE NEED FOR BETTER INFORMATION ON CURRENT HEALTH R&D

The thesis also makes suggestions for improving the availability of information that needs to be collected as part of health research priority setting processes. Health research priorities are commonly set by experts, who ground their decisions in information on what health research is needed, and information on what research is already being undertaken. This thesis concentrates on the latter – information on what health research is already being undertaken. To acquire detailed insight into the current health R&D landscape, different types of data need to be considered, such as data on R&D inputs (e.g. investments or human resources), R&D processes (e.g. clinical trials), R&D outputs (e.g. publications, patents, or products), and the impact of those outputs (e.g. on health or socio-economic status). All information sources that can currently provide such data have important limitations. Our knowledge of what health R&D is being conducted globally, where it is being conducted, by whom and how, is limited. By providing an investigation into what data are currently available, and what data are missing, this thesis presents a first step towards improving this situation.

Moreover, the thesis presents an exploration of how a relatively new type of data – registered clinical trial data – can inform health research priority setting processes. Over the past decade, several measures have been implemented to encourage principal investigators to register their clinical trials. Registration entails requesting an identification number for the clinical trial at a clinical trial registry and providing a minimum amount of information about the trial to the registry (such as on the intervention and the outcomes). This information is made publicly available by the registry and is passed on to the International Clinical Trials Registry Platform (ICTRP) at WHO. The ICTRP collects these data from fifteen clinical trial registries and provides a single point of access to registered clinical trial data from around the world. These registered clinical trial data can be used for a number of purposes. To date, clinical trials registration has been mainly advocated for three reasons: because it improves access to information on clinical trials for patients, healthcare workers and researchers; because it allows for steps to be taken against publication bias and selective outcome reporting; and for its potential to increase the accountability of those conducting clinical trial research. This thesis shows that registered clinical trial data can also be used to inform health research priority setting. Through two case studies, the thesis demonstrates that these data can be used to acquire broad insight into the health R&D that is currently being conducted in the world, as well as to acquire more detailed insights into ongoing health R&D in defined research areas. Therefore, registered clinical trial data have the potential to inform high-level policy directions for health R&D, as well as to inform lower-level decisions about R&D priorities for specific health problems. The utilization of registered clinical trial data for these purposes has several advantages: registries of clinical trials are the most complete source of data on what clinical trials are being conducted globally; the data are up-to-date, since the registered records of the trials are updated by investigators to reflect the current status of the trial; the database format and its public accessibility make the data highly searchable (as opposed to, for example, full protocols); and the registered records of the trials contain information that is complementary to the information presented in published articles.

However, there are also barriers that currently prevent the meaningful utilization of registered clinical trial data. The first barrier is completeness. Although registries of clinical trials constitute the most complete resource of information on the global distribution of clinical trial research, they are not complete enough – there are still trials that are not registered. Particularly in many low- and middle-income countries enforcement of registration remains weak. The second barrier is that extracting, aggregating and analysing registered trial data from the ICTRP currently requires significant manual labour. The ICTRP needs to automate such data aggregation and analysis, and make the results publicly available. The third barrier is the poor quality of the data in registered records of clinical trials. The reasons for poor data quality lie, at least in part, with the data recording formats of the registries (i.e. how the registries ask for the data) and with their quality control measures (i.e. if and how they check whether the data are of adequate quality). Hence, to increase the usability of registered clinical trial data, data recording formats and quality control measures at individual registries need to be improved.

A GLOBAL OBSERVATORY ON HEALTH R&D

At the World Health Assembly of May 2013 it was decided that a Global Observatory on Health R&D should be established. This is an important development with regard to the research presented in this thesis. The envisioned function of the Observatory is to set health research priorities at the global level comprehensively, systematically, and periodically. In that function, the Observatory is likely to provide an impetus for further development of methods for health research priority setting processes and for improving the availability of information that needs to be collected as part of such processes.
IMPLEMENTATION OF GLOBAL HEALTH RESEARCH PRIORITIES

Finally, this thesis reviews and discusses ways in which the implementation of global health research priorities could be improved. It argues that collaborative groups of health research funders should play a larger role in promoting coordination on global health research priorities than they currently do. It explains that the recent establishment of a Global Observatory on Health R&D offers possibilities for enhancing such coordination by providing a platform for funder collaboration. It also makes clear that there is a need for more far-reaching measures, particularly a mechanism for funding health research that is prioritized at the global level. At the same World Health Assembly where the establishment of a Global Observatory on Health R&D was approved, agreement was not reached on more far-reaching measures. They will be discussed again at the World Health Assembly in 2016.

CONCLUSION

In conclusion, this thesis explains that at present there is no system to set health research priorities comprehensively, systematically, and periodically at the global level. It shows that rigorous methods are available to establish high-quality health research priority setting processes, but that these methods are currently underused. It demonstrates that the information needed to appropriately prioritize the areas of greatest health R&D need is obtainable, but not systematically collected. Finally, it makes clear that there is an urgent need for greater collaboration in addressing global priorities for health research, but that such collaboration currently only takes place on an ad-hoc basis in selected areas. The recent establishment of a Global Observatory on Health R&D may help to address some of these issues. Until they are addressed, they remain missed opportunities to ameliorate the mismatch between the health R&D that is needed and the R&D that is undertaken.
Introduction
BACKGROUND ON HEALTH RESEARCH PRIORITY SETTING

Health problems are defined by the World Health Organization (WHO) as ‘a major cause of ill-health or health inequity, whether actual or prospective’. This definition includes diseases such as HIV or mental illness, risks to health such as obesity or poverty, and obstacles to effective systems performance such as unsafe care or inequitable financing of health services. Every year, approximately 6.5 trillion US dollars are spent combating the world’s health problems.

Health research and development (R&D) provides us with opportunities to mount a better response to health problems. There are different types of health research, and each type offers different opportunities for improving our health response. Research might measure the magnitude and distribution of a health problem; help to understand the causes of the problem; elaborate solutions; translate the solutions or evidence into policy, practice and products; or evaluate the impact of solutions. Some research takes place on an individual level (i.e. biomedical research or clinical research), other research takes place on a population level (i.e. epidemiological research or health systems research). Research that focuses on developing products can aim to develop a variety of different products, such as devices, medicines, vaccines, procedures or systems.

Every year, approximately 240 billion US dollars are spent globally on health R&D. The global health R&D system as we know it has led to many life-saving products and knowledge over the past century. Yet, the same system has been described as ‘broken’ for leaving important areas of research largely neglected. To this day, one of the most pressing global health problems is that there is a mismatch between the health R&D that is needed and that which is undertaken. This is exemplified most clearly by the lack of health R&D for populations in developing countries, often referred to as the ‘10/90 gap’. However, other research areas, too, have been repeatedly shown to constitute gaps in the R&D landscape. This becomes clear, for example, from the global lack of R&D for new antibiotics, the lack of appropriate children’s medicines (and other products), the gaps that exist in the R&D that is conducted for orphan diseases, the realization that some ‘neglected diseases’ are more neglected than others, and from studies that show that major funders of health R&D do not necessarily allocate research funding to where it is needed the most. Chapter 2 explores the mismatch between the health R&D that is needed and that which is undertaken in more detail.

To ameliorate this mismatch, there is a need for improved global health R&D governance – the field that is concerned with decision-making processes about what health R&D is conducted in the world. One component of global health R&D governance is health research prioritization. Health research priority setting processes are used by researchers and policymakers to help them make choices about what R&D to conduct or to invest in. Such
Introduction

processes can be organized locally, nationally, regionally, and globally. They can focus on one health problem, a group of health problems, or cover all health problems. The processes commonly combine the collection of background information on health and health research with expert opinion. The background information should consist of at least three components:

- Information on the magnitude and distribution of existing health problems
- Information on the need for new knowledge and/or products to address those problems
- Information on the health R&D that is already being undertaken

Unfortunately, this information is not always available. Globally, these three information needs, most is known about the magnitude and distribution of existing health problems owing to the Global Burden of Disease studies (although this information is also not without its limitations). Much less is known about what new knowledge and products are needed globally. These needs are currently not comprehensively and systematically assessed, and the information that is available is based largely on ad-hoc analyses in specific areas. The same holds true for what R&D is already being undertaken globally. Remarkably, our knowledge of what health R&D is being conducted, where it is being conducted, by whom and how, is very limited. Different indicators can be used to monitor what health R&D is being conducted: R&D inputs (e.g. investments), R&D processes (e.g. clinical trials or the R&D pipeline), R&D outputs (e.g. publications or products such as medicines), and R&D outcomes or impact (e.g. on health or socio-economic status). For all of these indicators, there are substantial information gaps, especially with regard to data from low- and middle-income countries.

This thesis will aim to advance the evidence base for global health R&D governance. It will do so by exploring how health research priority setting takes place at the global level, how it should take place, and how data on currently ongoing health R&D can inform global-level health research priority setting. It will focus specifically on investigating the value of utilizing a new source of information on R&D processes – registered clinical trial data – for this purpose. The scope of all these investigations will be limited to health research priority setting at the global level.

Before continuing to the next section – which will explain what registered clinical trial data are, where they come from, and what they can be used for – it is necessary to clarify several terms that are used in this thesis in relation to health research and health research priorities.

First, different terms are in use in the scientific discourse to describe health research. Besides the term ‘health research’ itself, there are the terms ‘research for health’ and ‘health research and development (R&D)’. Although these terms all have separate definitions, in practise their meanings are similar and they are used interchangeably. In some areas of research, researchers prefer one term, whereas in other areas, researchers prefer another. The literature around priority setting methods, for example, predominantly makes use of the terms ‘health research’ and ‘research for health’. Yet, the literature around gaps in the health research landscape, in which pharmaceutical product development often has a more prominent role, more often refers to ‘health R&D’. In this thesis, the use of these terms has been adapted in each chapter to be consistent with the prevailing terminology in the literature. In the Introduction and Discussion sections, I have mainly used the term ‘health R&D’.

Second, this thesis’s focus on global-level health research priority setting processes raises an important question: what are ‘global priorities’ for health R&D? Whose priorities are we talking about? In the international discourse on health R&D the knowledge and products that are generated by health R&D are increasingly framed as ‘global public goods’. Access to such knowledge and products is increasingly recognized as integral to the human right to health. This means that in terms of research beneficiaries, global priorities for health R&D imply a global population of end-users. In terms of research funders, global priorities for health R&D imply a globally-shared burden, which rests, at least in part, with the public sector.

BACKGROUND ON CLINICAL TRIALS REGISTRATION

The need for clinical trials registration was documented for the first time in 1974, when Mary Lasker called for a book, to be updated every six months, in which to register all cancer trials. She felt the availability of a list of all clinical trials would allow patients and doctors to inform themselves more adequately about trials in which enrolment could be possible. Not long after, Tom Chalmers also suggested the establishment of a database of all clinical trials, but for a different reason. He felt the registration of all clinical trials before enrolment of the first participant might prove useful for reducing bias in the reporting of clinical trials.

It took time before action was undertaken to heed these calls. The first publicly accessible clinical trial registries were only established towards the late nineties. In subsequent years many other registries on different continents followed. With these registries, investigators can ‘register’ their clinical trials. Registration entails that each trial is assigned a unique identification number. In addition, investigators are required to submit to the registry a minimum amount of information about their trial (Box 1.1). The registries make these registered clinical trial data publicly available on the internet so they can be accessed by patients, healthcare workers and researchers.

Due to the many different clinical trial registries at which registration was possible in the early 2000s, registered clinical trial data were dispersed, making it difficult to access all the available
information. Therefore, in 2005, the International Clinical Trials Registry Platform (ICTRP) was established at WHO. The ICTRP created a platform that linked all clinical trial registries, with the aim of ensuring a single point of access to information on all clinical trials conducted globally. Today, the ICTRP combines data from fifteen different national and regional clinical trial registries, offering access to information on more than 200,000 clinical trials.

Clinical trials registration is now widely accepted to be a scientific and ethical responsibility. Crucial to this development has been the increased enforcement of clinical trials registration over the past decade, through national legislation on registration, policies by journal editors and publishers making registration a prerequisite for publication, ethics committees and national research ethics oversight agencies requiring registration as part of procedures for ethics approval, policies by funders making registration a prerequisite for grant approval, codes of research practice that recommend trial registration, such as the SPIRIT 2013 and CONSORT 2010 statements, statements from professional organizations such as the declaration of Helsinki and self-regulation by universities and the pharmaceutical industry.

The raison d’être for clinical trials registration is that it increases transparency in clinical trial conduct and reporting. To date, largely in line with the early calls by Mary Lasker and Tom Chalmers, clinical trials registration has mainly been advocated for three reasons:

1. Because it improves access to information on clinical trials for patients, healthcare workers and researchers, thus improving appropriate enrolment in trials, knowledgeability of trials, and collaboration on trials.
2. Because it allows for steps to be taken against publication bias and selective outcome reporting. Through registration it becomes possible to compare published trials with registered trials and published outcomes with the outcomes that were registered before the trial started recruiting participants.
3. For its potential to increase the accountability of those conducting clinical trial research. This has become particularly relevant after several examples of misconduct by clinical trial sponsors and investigators, including the fabrication, falsification and withholding of data, and not obtaining ethics approval and informed consent for trials.

In this thesis, I will explore whether clinical trials registration might be able to serve a fourth purpose: to inform health research priority setting processes.

**RATIONALE**

One of the most pressing global health problems today is that there is a mismatch between the health R&D that is needed and the R&D that is undertaken. To help address this problem there is a need for increased scrutiny of global-level health research priority setting processes.

One important impediment to effective health research prioritization at the global level is the lack of available information on what health R&D is being conducted in the world, where it is being conducted, by whom and how. More research is needed on what data sources are available, what their strengths and limitations are, and what is needed to increase their usefulness.

Registered clinical trial data may constitute a valuable, new source of information on what health R&D is being conducted in the world. Enforcement of clinical trials registration has increased in recent years and databases of registered clinical trials have grown substantially in size. The ICTRP is the most inclusive database of registered clinical trials and provides access to data from more than 200,000 trials. For each trial, a substantial amount of information is available. The strengths and limitations of utilizing registered clinical trial data for gaining insight into what health R&D is being conducted in the world have, to date, not been duly scrutinized.

**BOX 1.1. THE WHO TRIAL REGISTRATION DATA SET (TRDS)**

The 20-item WHO Trial Registration Data Set (TRDS) outlines the minimum amount of information about a trial that must appear in a register for a given trial to be considered fully registered.

1. Primary Registry and Trial Identifying Number
2. Date of Registration in Primary Registry
3. Secondary Identifying Numbers
4. Source(s) of Monetary or Material Support
5. Primary Sponsor
6. Secondary Sponsor(s)
7. Contact for Public Queries
8. Contact for Scientific Queries
9. Public Title
10. Scientific Title
11. Countries of Recruitment
12. Health Condition(s) or Problem(s) Studied
13. Intervention(s)
14. Key Inclusion and Exclusion Criteria
15. Study Type
16. Date of First Enrollment
17. Target Sample Size
18. Recruitment Status
19. Primary Outcome(s)
20. Key Secondary Outcomes
AIM AND OBJECTIVES

The aim of this thesis is to examine global-level health research priority setting processes, to explore how data on currently ongoing health R&D can inform those processes, and to investigate specifically the utilization of registered clinical trial data for that purpose.

The objectives of this thesis are:
1. to examine health research priority setting processes at the global level and identify good practices for such processes;
2. to explore how data on currently ongoing health R&D, in particular registered clinical trial data, can inform health research priority setting processes;
3. to evaluate what barriers there are to the meaningful utilization of registered clinical trial data and how these may be mitigated.

THESIS OUTLINE

The structure of this thesis is outlined in Figure 1.1.

Figure 1.1. Overview of the outline of the thesis by aim, objectives and chapters.

AIM
To examine global-level health research priority setting processes, to explore how data on currently ongoing health R&D can inform those processes, and to investigate specifically the utilization of registered clinical trial data for that purpose

OBJECTIVE 1
To examine health research priority setting processes at the global level and identify good practices for such processes

Chapters 2, 3, 4, 5

OBJECTIVE 2
To explore how data on currently ongoing health R&D, in particular registered clinical trial data, can inform health research priority setting processes

Chapters 6, 7, 8, 9

OBJECTIVE 3
To evaluate what barriers there are to the meaningful utilization of registered clinical trial data and how these may be mitigated

Chapters 10, 11, 12

Notes: The overview does not include Chapter 1, the Introduction, and Chapter 13, the Discussion.

OBJECTIVE 1
To examine health research priority setting processes at the global level and identify good practices for such processes

Chapter 2 describes the broader global health R&D governance context of this thesis. The chapter provides an overview of the mismatch between the health R&D that is needed and that which is undertaken. It presents a detailed description of the nature of this problem and identifies the different causes that have led to health research priorities either not being established, or not being addressed. In doing so, it provides an extended rationale for this thesis and makes clear why increased scrutiny of global-level health research priority setting processes is needed.

Chapter 3 provides further insight into how health research priorities are established at the global level. The methods used to set priorities are assessed for all health research priority setting exercises that were organized or coordinated through WHO headquarters from 2005 to 2010.

Chapter 4 provides insight into how health research priorities should be established at the global level, addressing the need for normative work in the area of health research priority setting. The chapter describes the development of a checklist for health research priority setting, based on a literature review and interviews with key stakeholders.

Chapter 5 discusses how research priorities should be implemented at the global level, focusing particularly on the shared responsibility that funders of health research carry in this regard.

OBJECTIVE 2
To explore how data on currently ongoing health R&D, in particular registered clinical trial data, can inform health research priority setting processes

Chapter 6 provides a comprehensive mapping of all available data sources on health R&D and assesses the data availability and limitations of the available sources. The chapter makes clear that registered clinical trial data form one part of the puzzle that needs to be completed in order to obtain complete insight into the composition of the global health R&D landscape.

Chapters 7, 8 and 9 present the results of two case studies that investigate the strengths and limitations of utilizing registered clinical trial data as an information resource for health research priority setting processes. The two case studies have different scopes, to allow for evaluation of the different ways in which clinical trial data may be utilized for this purpose.
Chapter 7 and 8 present the results of the first case study. This study has a broad scope and investigates a 5% sample of all interventional and actively recruiting trials on the ICTRP. Chapter 7 describes in detail the methods of the study, including its strengths and limitations, and provides insight into the global distribution of clinical trial research. Chapter 8, based on the same study, presents an investigation of the global distribution of paediatric clinical trial research. Chapter 9 presents the results of this second case study. This study has a narrow scope and analyses all clinical trials that investigate pharmacokinetic profiles of medicines in children. The chapter examines the results of the study in light of a list of pharmacokinetic research priorities for off-patent paediatric medicinal products established by the European Medicines Agency.

OBJECTIVE 3
To evaluate what barriers there are to the meaningful utilization of registered clinical trial data and how these barriers may be mitigated

Under this objective, barriers to the meaningful utilization of data from registered clinical trials are explored. The chapters focus on one barrier in particular: poor data quality. Chapter 10 investigates the quality of information in various data fields of registered records of clinical trials. Chapter 11 presents a re-analysis of the study in Chapter 10, conducted four years later. It assesses whether the quality of registration has changed over time. Chapter 12, lastly, zooms in on one data element and investigates in more detail what the causes are for poor data quality in registered records of clinical trials.

Chapter 13 is the concluding chapter of this thesis. It discusses the thesis’s contributions and limitations. Additionally, it provides an overview of recent developments and next steps in the area of global health R&D governance and makes recommendations for future research.

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“Two things should not be seen while they are being made – sausages and public policy.”

Otto von Bismarck

OBJECTIVE 1
To examine health research priority setting processes at the global level and identify good practices for such processes
Based on

Viergever RF.

The mismatch between the health R&D that is needed and the R&D that is undertaken: an overview of the problem, the causes, and solutions.

The mismatch between the health research and development (R&D) that is needed and that which is undertaken first demonstrated in 1990, when it was shown that less than 10% of global health research expenditure was spent on the health problems of developing countries, which then represented more than 90% of the world’s burden of preventable mortality (Figure 2.1). This disparity later became well-known as the ‘10/90-gap’. The nature of the 10/90-gap has changed substantially since 1990: the distribution of the global disease burden has changed; overall global funding for health R&D has increased from 30 billion USD in 1986 to 240 billion USD in 2010; there are many more and new types of actors involved in health R&D and a variety of new approaches to innovation have been suggested and tested in recent years, and continue to be developed, to encourage action on previously neglected areas of health R&D. However, even though the nature of the 10/90-gap has changed since 1990, the gap itself very much remains to this day.

The 10/90-gap is a prominent expression of a broader problem which is better described as one of ‘neglected populations’. This neglect can be seen in the lack of R&D for diseases that predominantly affect developing countries (the ‘neglected diseases’), in the lack of R&D that addresses the specific needs of developing countries in relation to diseases with a global incidence, and in the lack of development of affordable medicines for all. But the problem of neglect extends beyond the developing world, as becomes clear from the global lack of R&D for new antibiotics, appropriate children’s medicines (and other products), and orphan diseases. In addition to neglected populations there are neglected products. R&D is generally more focused on the development of drugs and vaccines than on the development of diagnostics or platform technologies (technologies that can potentially be applied to different diseases and products). Moreover, for specific diseases, some products are neglected in terms of R&D, whereas others are not.

Besides the discrete distinction between neglected and non-neglected areas of health R&D, there is a broader issue with the global distribution of health R&D as part of the mismatch. ‘Needs-driven’ R&D is not necessarily characterized by a linear relationship between disease burden and R&D funding, since burden of disease is just one of the factors that determine health R&D need (see Box 2.1 for what determines health R&D need). In assessing health R&D needs, it is necessary to be specific about the knowledge and/or products that are

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**ABSTRACT**

One of the most pressing global health problems is that there is a mismatch between the health research and development (R&D) that is needed and that which is undertaken. The dependence of health R&D on market incentives in the for-profit private sector and the lack of coordination by public and philanthropic funders on global R&D priorities have resulted in a global health R&D landscape that neglects certain products and populations and is characterized, more generally, by a distribution that is not ‘needs-driven’. This chapter provides an overview of the mismatch and its causes.

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**THE PROBLEM**

The mismatch between the health research and development (R&D) that is needed and that which is undertaken was first demonstrated in 1990, when it was shown that less than 10% of global health research expenditure was spent on the health problems of developing countries, which then represented more than 90% of the world’s burden of preventable mortality (Figure 2.1). This disparity later became well-known as the ‘10/90-gap’. The nature of the 10/90-gap has changed substantially since 1990: the distribution of the global disease burden has changed; overall global funding for health R&D has increased from 30 billion USD in 1986 to 240 billion USD in 2010; there are many more and new types of actors involved in health R&D and a variety of new approaches to innovation have been suggested and tested in recent years, and continue to be developed, to encourage action on previously neglected areas of health R&D. However, even though the nature of the 10/90-gap has changed since 1990, the gap itself very much remains to this day.

The 10/90-gap is a prominent expression of a broader problem which is better described as one of ‘neglected populations’. This neglect can be seen in the lack of R&D for diseases that predominantly affect developing countries (the ‘neglected diseases’), in the lack of R&D that addresses the specific needs of developing countries in relation to diseases with a global incidence, and in the lack of development of affordable medicines for all. But the problem of neglect extends beyond the developing world, as becomes clear from the global lack of R&D for new antibiotics, appropriate children’s medicines (and other products), and orphan diseases. In addition to neglected populations there are neglected products. R&D is generally more focused on the development of drugs and vaccines than on the development of diagnostics or platform technologies (technologies that can potentially be applied to different diseases and products). Moreover, for specific diseases, some products are neglected in terms of R&D, whereas others are not.

Besides the discrete distinction between neglected and non-neglected areas of health R&D, there is a broader issue with the global distribution of health R&D as part of the mismatch. ‘Needs-driven’ R&D is not necessarily characterized by a linear relationship between disease burden and R&D funding, since burden of disease is just one of the factors that determine health R&D need (see Box 2.1 for what determines health R&D need). In assessing health R&D needs, it is necessary to be specific about the knowledge and/or products that are

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*R&D is defined by the Organisation for Economic Co-operation and Development (OECD) as: ‘Research and experimental development comprise creative work undertaken on a systematic base in order to increase the stock of knowledge, including knowledge about man, culture and society, and the use of this knowledge to devise new applications.’ R&D is generally subdivided into basic research, applied research and experimental development. Health R&D includes fields such as epidemiology, health services and health systems research, and health-related social research.*
The mismatch between the health R&D that is needed and the R&D that is undertaken

Although there are also indications in other areas, such as R&D for orphan drugs, that there are some diseases that are more neglected than others, analyses such as the G-FINDER reports, which aggregate all global funding towards a set of diseases, are rare. Because only few funders publicly report disaggregated statistics on health R&D expenditures, and because of a lack of uniformity in the use of R&D classification systems across different funders, such analyses are complex and resource-intensive.

Figure 2.1.
The figure from the report of the Commission on Health Research for Development that formed the basis for the later coined term the ‘10/90-gap’ (re-printed by permission of Oxford University Press, USA)

Table 2.1.
Distribution of global health R&D funding across neglected diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>R&amp;D funding 2011 (million US$)</th>
<th>Global BoD (million DALYs)</th>
<th>R&amp;D funding in US$ / Global DALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - HIV</td>
<td>1117</td>
<td>81.5</td>
<td>13.7</td>
</tr>
<tr>
<td>2 - Malaria</td>
<td>596</td>
<td>82.7</td>
<td>7.2</td>
</tr>
<tr>
<td>3 - Tuberculosis</td>
<td>584</td>
<td>49.4</td>
<td>11.8</td>
</tr>
<tr>
<td>4 - Dengue</td>
<td>249</td>
<td>0.8</td>
<td>301.7</td>
</tr>
<tr>
<td>5 - Diarrhoeal diseases</td>
<td>169</td>
<td>89.5</td>
<td>2.0</td>
</tr>
<tr>
<td>6 - Kinetoplastids</td>
<td>142</td>
<td>4.4</td>
<td>32.0</td>
</tr>
<tr>
<td>7 - Bacterial pneumonia &amp; meningitis</td>
<td>107</td>
<td>68.0-104.9</td>
<td>1.0-1.6</td>
</tr>
<tr>
<td>8 - Helminths (worms &amp; flukes)</td>
<td>90</td>
<td>12.3</td>
<td>7.3</td>
</tr>
<tr>
<td>9 - Salmonella infections</td>
<td>48</td>
<td>17.1</td>
<td>2.8</td>
</tr>
<tr>
<td>10 - Trachoma</td>
<td>10</td>
<td>0.3</td>
<td>31.1</td>
</tr>
<tr>
<td>11 - Leprosy</td>
<td>8</td>
<td>0.006</td>
<td>1400.9</td>
</tr>
<tr>
<td>12 - Buruli ulcer</td>
<td>6</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>13 - Rheumatic fever</td>
<td>1</td>
<td>10.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Notes: Table is based on Table 2 from the G-FINDER report 2012, which reports on global R&D funding for 31 neglected diseases. ‘Neglected diseases’ are defined in this report as diseases that disproportionally affect people in developing countries, for which there is a need for new products, and for which there is market failure. The list of 31 diseases includes HIV, tuberculosis and malaria, and thus adheres to a different definition of neglected diseases than WHO. Burden of disease (BoD) data are from the Global Burden of Disease (GBD) study 2010. DALY = disability-adjusted life years.

Global BoD for bacterial pneumonia and meningitis is displayed as a range because ‘other LRIs’ and ‘other meningitis’ in the GBD study 2010 were not sub-specified into viral or bacterial pathogens. The lower limit represents the BoD without the ‘other’ categories, while the upper limit includes the ‘other categories’.

Global BoD data for buruli ulcer were not available.

needed for each health problem and to take into account differences in need between different populations. However, on the presumption that R&D funding is responsive to the scale of a health problem, a degree of correlation between the burden of a health problem and R&D funding can be expected. Working from this presumption provides us with a crude approach to assessing the global distribution of health R&D funding (as was done, for example, with the 10/90-gap). Within the area of neglected diseases, the Global Funding of Innovation for Neglected Diseases (G-FINDER) reports have shown that of 31 neglected diseases, some are more neglected than others. There are three ‘top tier’ diseases which each receive one-third to one-sixth of total global neglected disease R&D funding, a number of ‘second tier’ diseases which each receive 1% to 8% of total funding, and several ‘third tier’ diseases, which are the most poorly funded and receive less than 0.5% of global funding each. Table 2.1 shows the neglected diseases from the most recent G-FINDER report in terms of funding and in terms of global burden of disease. In interpreting this table, it is important to remember that health R&D need depends on more than burden of disease (Box 2.1). Nonetheless, the findings from G-FINDER make clear the variations in R&D investments for these diseases. Moreover, the G-FINDER reports have shown that R&D investments for a particular disease are not necessarily allocated towards developing the knowledge or products that are most needed for that disease. It is concluded that ‘R&D funding is often poorly matched with disease needs and scientific and technical possibilities.’
The mismatch between the health R&D that is needed and the R&D that is undertaken

However, when we look at individual R&D funders’ investment portfolios, marked variations in funding for similar diseases also become apparent. Brower argued in 2005 that ‘research funding is not necessarily allocated to those who need it most’ by showing the variation in R&D funding for different diseases by the US National Institutes of Health (NIH). Table 2.2 shows an updated list of US NIH R&D funding for different cancers in the US and makes clear the variation in R&D funding per US DALY for these diseases.

Looking at research investments is only one way of measuring what R&D is being undertaken. Other R&D indicators can also be reviewed, such as the number of research articles or ongoing clinical trials. By doing so, Nwaka et al, for example, showed recently with regard to health R&D in Africa that ‘diseases disproportionately affecting Africa are under-prioritized’. Table 2.3 is based on some of their results and makes clear for the five diseases with the highest burden from Table 2.1 that the variations in numbers of African publications and African clinical trials roughly correspond to the variations in global R&D funding. In another example, Dear et al show that variations in the R&D that is conducted for different cancers exist in other countries, too, by demonstrating that in Australia ‘four of the five cancers that result in the greatest burden of disease had relatively few clinical trials’.

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**Table 2.2.** Distribution of US National Institutes of Health (NIH) funding across cancers

<table>
<thead>
<tr>
<th>Disease</th>
<th>R&amp;D Funding 2011 (Million US$)</th>
<th>US BoD (Thousand DALYs)</th>
<th>R&amp;D Funding in US$ / US DALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>284</td>
<td>225</td>
<td>1262.0</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>143</td>
<td>114</td>
<td>1253.7</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>715</td>
<td>612</td>
<td>1167.4</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>138</td>
<td>145</td>
<td>951.8</td>
</tr>
<tr>
<td>Colo-Rectal Cancer</td>
<td>313</td>
<td>542</td>
<td>577.4</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>74</td>
<td>138</td>
<td>5370</td>
</tr>
<tr>
<td>Uterine Cancer</td>
<td>40</td>
<td>75</td>
<td>510.0</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>112</td>
<td>238</td>
<td>471.1</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>221</td>
<td>1248</td>
<td>1771</td>
</tr>
</tbody>
</table>

Notes: Table based on Table 1 from Brower (2005). US burden of disease (BoD) Data were derived from the WHO Global Burden of Disease (GBD) data from 2004. DALYs = disability-adjusted life years.

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**Table 2.3.** Distribution of African R&D funding across cancers

<table>
<thead>
<tr>
<th>Disease</th>
<th>R&amp;D Funding (Million US$)</th>
<th>Publications (no.)</th>
<th>Clinical Trials (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>284</td>
<td>225</td>
<td>1262.0</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>143</td>
<td>114</td>
<td>1253.7</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>715</td>
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<td>Ovarian Cancer</td>
<td>138</td>
<td>145</td>
<td>951.8</td>
</tr>
<tr>
<td>Colo-Rectal Cancer</td>
<td>313</td>
<td>542</td>
<td>577.4</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>74</td>
<td>138</td>
<td>5370</td>
</tr>
<tr>
<td>Uterine Cancer</td>
<td>40</td>
<td>75</td>
<td>510.0</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>112</td>
<td>238</td>
<td>471.1</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>221</td>
<td>1248</td>
<td>1771</td>
</tr>
</tbody>
</table>

Notes: Table based on Table 1 from Brower (2005). US burden of disease (BoD) Data were derived from the WHO Global Burden of Disease (GBD) data from 2004. DALYs = disability-adjusted life years.

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**Figure 2.2.** Health R&D need is determined by: A) existing health problems, B) the need for new knowledge and/or products, and C) the health R&D that is already being undertaken

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**BOX 2.1. WHAT IS ‘HEALTH R&D NEED’?**

What determines whether there is a need for health R&D? To determine health R&D need it is necessary to first evaluate which health problems exist that cause a burden of disease (Figure 2.2). The more prominent the health problem, the larger the potential impact of R&D. The scale of different health problems are regularly assessed as part of the Global Burden of Disease studies. Secondly, it is necessary to determine the need for new knowledge and/or products (including devices, medicines, vaccines, procedures and systems) for a given health problem. Finally, to determine health R&D need, we must also take into account what health R&D is already being undertaken.

With all these steps it is critical to be specific and account for potential differences in health R&D need between different populations, such as geographical regions, age groups and socio-economic sub-groups.

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**Evaluation of existing health problems**

**Evaluation of need for new knowledge and/or products**

**Evaluation of R&D that is already being undertaken**

**Health R&D need**
The mismatch between the health R&D that is needed and the R&D that is undertaken

Finally, there are problems with realizing a coordinated response to established global priorities for health R&D. The current global health R&D system relies strongly on market incentives. About 60% of all health R&D funding comes from the for-profit private sector. However, when market incentives drive innovation, R&D that is profitable will be preferred, with the neglect of populations and products that are not profitable as a result.

Further, market incentives even drive the development of products that may be profitable but that offer little or no additional therapeutic value (‘me-too’ drugs).

Finally, a lack of open innovation is inherent to a competitive privatized system and constitutes an impediment to the efficiency and ethicality of the R&D system. This was recently demonstrated by the reluctance of pharmaceutical companies, with one exception (GlaxoSmithKline), to join the AllTrials campaign (an initiative that calls for all clinical trials to be registered and all trial results to be reported).

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Table 2.3.
Distributions of research articles and clinical trial research across five neglected diseases in Africa

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of articles with at least one African author / million African DALY</th>
<th>Number of trials recruiting in Africa / million African DALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoeal diseases</td>
<td>91</td>
<td>0.2</td>
</tr>
<tr>
<td>Lower respiratory infections and meningitis</td>
<td>10.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Malaria</td>
<td>59.7</td>
<td>6.6</td>
</tr>
<tr>
<td>HIV</td>
<td>53.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>82.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Notes: To demonstrate how the distribution of R&D can be measured using different R&D indicators, numbers of African research articles and African clinical trials are related to African burden of disease for the five diseases with the highest burden of disease in Table 2.1. Numbers were calculated from Nwaka et al (2010). DALYs = disability-adjusted life years.

THE CAUSES

This section aims to describe what has caused the mismatch between the health R&D that is needed and that which is undertaken. A rational approach to establishing and funding a global agenda for health R&D is illustrated in Box 2.2. In reality, there are problems with every step of this approach, together forming the reasons that the mismatch exists.

First, there is no system to comprehensively, systematically and periodically map what health R&D is needed globally (step 1). Health R&D needs, as detailed in Box 2.1, are determined by the burdens of existing health problems, by the need for new knowledge and/or products, and by the R&D that is already being undertaken. Although substantial progress has been made in evaluating the burdens of existing health problems, the need for new knowledge and/or products is only assessed on an ad-hoc basis and for a selected number of diseases (e.g. 9,31–33). Our knowledge of what health R&D is being conducted, where it is being conducted, by whom and how, is also very limited. Moreover, there is currently no accepted approach for comparing health R&D needs across different health problems.

Second, although health R&D priorities are regularly established for specific diseases and countries, there is currently no system to facilitate the prioritization of all health R&D needs and the formulation of ‘best buys’ in health R&D globally (step 2).

Finally, there are problems with realizing a coordinated response to established global priorities for health R&D (steps 3 and 4). The current global health R&D system relies strongly on market incentives. About 60% of all health R&D funding comes from the for-profit private sector. However, when market incentives drive innovation, R&D that is profitable will be preferred, with the neglect of populations and products that are not profitable as a result. Market incentives even drive the development of products that may be profitable but that offer little or no additional therapeutic value (‘me-too’ drugs). Furthermore, few measures exist to ensure that products are affordable, which is an ever-present challenge for universal access to medicines when one considers that the great majority of the global burden of disease is carried by populations in developing countries. Finally, a lack of open innovation is inherent to a competitive privatized system and constitutes an impediment to the efficiency and ethicality of the R&D system. This was recently demonstrated by the reluctance of pharmaceutical companies, with one exception (GlaxoSmithKline), to join the AllTrials campaign (an initiative that calls for all clinical trials to be registered and all trial results to be reported).

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BOX 2.2.
A RATIONAL APPROACH FOR ESTABLISHING AND FUNDING A GLOBAL HEALTH R&D AGENDA

A rational approach for establishing and funding a global health R&D agenda consists of four steps (based on 8,34):

1. Identify health R&D needs
   What are the gaps in the health R&D landscape that need to be addressed? For such identification we need (see Box 2.1):
   • Evaluation of existing health problems
   • Evaluation of need for new knowledge and/or products
   • Evaluation of health R&D that is already being undertaken

2. Prioritize
   Which health R&D needs, if addressed, would result in the highest health return on investment?
   Decision criteria:
   • Expected health benefit
   • Expected costs
   • Expected feasibility

3. Coordinate
   Coordinate among funders to agree on a common health R&D agenda.

4. Fund
   Fund the health R&D agenda.
Public and philanthropic donors are responsible for the remaining 40% of all health R&D funding. In the area of neglected disease R&D, where more than 80% of R&D funding is allocated by these funders, the G-FINDER reports consistently show under-funding of priority areas of R&D and high-burden diseases. How can it be that such gaps remain when public and philanthropic funders distribute the majority of funding?

One important reason is that there is not yet an accepted system of accountability for global health R&D needs. It is becoming increasingly recognized that the outputs of health R&D should be viewed as global public goods, meaning that all knowledge and products resulting from health R&D should be adapted and accessible to a global population of end-users and that funding health R&D should be a globally-shared burden. Yet, currently, there is no global governance arrangement that makes explicit the shared accountability that such views imply. In the absence of a concrete shared vision of accountability, the Bamako call to action on research for health suggests that in the current system all funders of health R&D are jointly responsible to ‘better align, coordinate, and harmonize the global health research architecture’. However, in practice there are problems with regard to the degree to which these funders are accountable for global health R&D needs. The public and philanthropic health R&D funding landscape is diverse and includes national public funders of health R&D (such as health ministries or government research organizations), distributors of Official Development Assistance (ODA) (such as development or foreign affairs ministries), multilateral funding agencies, and philanthropic funders of health R&D. National public funders of health R&D have often been established under national laws, have nationally focused remits, and are accountable to the parliament of the country they are based in. Hence, it is questionable whether they can be expected to fund health R&D that is globally relevant, but, for example, not of relevance to the country they are based in. Distributors of ODA do often have a global focus, but their contributions to overall global health R&D are relatively small as compared to funding by national public funders of health R&D (neglected disease R&D funding in the US from 2000 to 2010, for example, was funded predominantly by the NIH (87%) and much less so by the US Agency for International Development (USAID) (6%) and the Department of Defense (DoD) (6%)23,46). The same is true for multilaterals. In addition, multilaterals are often dependent on earmarked funding, and several multilaterals have remits that are limited to a specific set of diseases. Philanthropic funders of health R&D may also have a global focus, but given that they are privately funded their accountability for global health R&D needs is, at best, uncertain. Tensions between global and national level priorities that arise because of the increasingly globalized nature of R&D, while most research funding is provided at a national level, are not unique to health.

Another important reason for the persistent nature of gaps in the global health R&D landscape is the lack of coordination by public and philanthropic funders on health R&D priorities. Given the fragmented funding landscape, enhanced coordination between funders on shared R&D priorities is greatly needed. However, such coordination currently only occurs selectively in particular areas. There is no global ‘forum’ where funders comprehensively and periodically discuss priority health R&D needs and how to address those needs in a coordinated manner.

Finally, R&D funding allocation decisions by public and philanthropic funders, whether they have a national or a global remit, may be influenced by factors other than the need for health R&D. Such factors include: the testimonials of patient advocacy groups or organizations with disease-specific mandates and advocacy and/or fundraising activities – ‘the squeaky wheel gets the grease’, as Brower suggests; the presence of policy frameworks and funding mechanisms that prioritize specific diseases; preferences of researchers (with most funders a large part of the research that is funded is investigator-initiated and some do not prioritize research areas at all); the existence of trusted R&D groups, the institutionalization of research topics, the attractiveness of research results and the potential for publication contribute; the national values, interests and political dynamics of the country in which the funder is based; global values and political dynamics; community and media attention; and funder perceptions, preferences and accountabilities. Given these diverse influences, there is a strong need for transparency from public and philanthropic health R&D funders on precisely what health R&D they fund and what their decision mechanisms are for funding allocation. Funders themselves recognize the need for such transparency, as becomes clear from a recent joint statement from several large health R&D funders on the importance of sharing research data. Unfortunately, individual funders that provide publicly accessible statistics on past funding for different health and research categories are still an exception rather than a rule, and funders continue to apply a kaleidoscope of different research classification systems, making aggregate analysis of what funders fund exceedingly problematic.

CONCLUSION

There is a mismatch between the health R&D that is needed globally and the R&D that is undertaken. The global landscape of health R&D shows gaps; there are neglected populations and products. Besides the discrete distinction between neglect and non-neglect, there are marked variations in the amount of R&D that is conducted for different health problems. Finally, the R&D that is undertaken for a particular health problem does not always match the knowledge or product development that is most needed for that problem. These problems are caused by the profit-based nature of the private health R&D sector and by problems around accountability, prioritization and coordination in the public and philanthropic health R&D sector.
ACKNOWLEDGEMENTS
I am indebted to Rob Baltussen, Koos van der Velden, Karin Rademaker, Eric Budgell and Katrina Perehudoff for reviewing drafts of this paper.

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The mismatch between the health R&D that is needed and the R&D that is undertaken

...
Health research prioritization at WHO: An overview of methodology and high level analysis of WHO led health research priority setting exercises

Based on
INTRODUCTION

Setting priorities for research is a complex process. Although there are several tools available to guide this process, there is general consensus that there can be no best practice for research priority setting, due to contextual differences between individual priority setting exercises. This project assessed what kind of methodologies and mechanisms were employed by World Health Organization (WHO) staff in setting research priorities since 2005. Because the assessment was in part based on expert consultation, insight was obtained into the need for guidance on the process of research priority setting.

Recently, the report of the WHO Expert Working Group on Research and Development Financing was completed. Inter alia, this report discusses possible mechanisms for increased coordination of research and development (R&D) on a global level. It proposes a globally coordinated approach to R&D, involving three key elements: coordination in the identification of priorities for action, coordination in the distribution of research among various entities and coordination in the financing of R&D. To inform possible next steps on mapping and prioritizing global R&D, this project also assessed the volume of health research priority setting exercises led by WHO headquarters (HQ) since 2005 and analysed these per health area. The inclusive nature and global scope of research priority setting at WHO make an analysis of WHO led exercises a plausible surrogate and a useful precursor for a potential global, more comprehensive evaluation.

METHODS

Data collection

All information products containing research priorities, a research agenda or gaps in R&D that were led by WHO HQ and produced since 2005 were collected. Information products were collected using a three-step process that was meant to minimize the possibility of missing any relevant information products:

1. A search of the WHO Library Database (WHOLIS) was performed. The following keywords were used: (research AND agenda) OR (research AND priorities) OR (research AND priority). Information products originating from the year 2005 or later that were found were scanned for the presence of research priorities, a research agenda or gaps in R&D.

2. All information products produced since 2005 in ‘publications’ sections of departmental websites were manually scanned for the presence of research priorities, a research agenda or gaps in R&D.

EXECUTIVE SUMMARY

As an initial step towards mapping and identifying research priorities globally, this report describes a review of health research priority setting exercises that have been organized or coordinated through the World Health Organization (WHO) headquarters since 2005. The majority of these exercises are undertaken with a view to identifying global health research priorities and usually draw on a wide range of stakeholders. Hence, the priorities that have been set by these exercises can be viewed as indicative of global health research priorities. The review analysed methodologies used to prioritize research and assessed the number of research priority setting exercises that were performed per health area.

This work found that there is a wide variety of research priority exercises undertaken at WHO. The majority of these exercises has been in the area of infectious and communicable diseases. In order to identify a global view it remains to be decided whether a meta-analysis or review of these exercises would be appropriate as a summary of global priorities or if a specific global exercise needs to be undertaken. A review of methods used in the prioritization exercises indicates there can be no gold standard or best practice in setting research priorities, but that there is a need and an expressed demand for normative work in this area.

The original version of this report contains several sections that are not relevant for this thesis. These sections were omitted from this chapter. (*)
3. Departments were contacted to confirm information products found and asked to provide any missing information products containing research priorities, a research agenda or gaps in R&D. Information products from before 2005 were included if they were indicated to still be relevant today. Information products since 2005 were omitted if they were indicated to be obsolete.

Assessment of employed methods
A quality assessment framework was developed that assessed all information products on key methodological approaches in setting research priorities. For every information product that was found, nine questions were answered (see Table 3.1).

Assessment of volume of research priority setting per health area
To acquire an overview of the volume of priority setting exercises per health area, information products were categorized according to the classification scheme of health topics as used by the WHO electronic publishing process (ePub). This scheme was developed by the WHO Web team and the WHO Library, combining terms from Medical Subject Headings (MESH), the United Nations Bibliographic Information System (UNbis), WHO specific terms and DeCS (Health Sciences Descriptors) and adapted by the WHO Press for electronic publishing purposes. The scheme was chosen because of its inclusive nature, encompassing all possible health topics that are subjects of research at WHO. As used in the electronic publishing process, each information product can only have one category. We allowed for multiple categories per information product.

Limitations
The study was bound by several limitations. Firstly, although we were systematic in our search strategy for information products that discussed research priority setting, it is possible that we missed certain information products, especially those in the form of grey literature or meeting notes. We have attempted to limit the number of missed information products by confirming our findings with representatives of all WHO HQ departments.

Secondly, in applying the quality assessment framework, we were dependent on the information provided in the information products. This limited the aspects of priority setting methods that we could assess. For example, an evaluation of how many priority setting exercises used literature review would have been an interesting outcome. However, due to

the large differences in terminology used and the lack of clarity surrounding the term ‘review’ in many information products, we decided to omit this evaluation.

Thirdly, there was large variation among different information products in the scope of established research priorities. For example, one exercise might look at research priorities for malaria globally, while another focuses on research priorities for preventive measures in the form of bed nets in a certain region. This makes comparison of research priorities difficult and limits the implications of quantitative analyses. We have attempted to remediate this issue by presenting separate results for information products whose main purpose was research priority setting.

Fourthly, we noticed during the assessment that definitions for research priority setting, research agenda setting and R&D or knowledge gap analysis are often used interchangeably. Although these definitions imply different things, we therefore chose to analyse information products discussing any of these concepts as one group.

Fifthly, this assessment limits itself to exercises led by WHO HQ since 2005. Therefore, the assessment cannot be taken as a true measure of the global situation. However, because the majority of priority setting exercises were undertaken with a view to identifying global health research priorities and usually draw on a wide range of stakeholders, these exercises can be viewed as indicative of global priorities and a review of their methodologies and resultant recommendations can inform any potential for undertaking a bespoke global exercise.

RESULTS
Catalogue
230 information products were found. A catalogue of these information products was created. The catalogue is intended to be a ‘living’ document and allows for periodical updates. The results as presented here are based on the catalogued information products on 20 April 2010.

Assessment of employed methods
The quality assessment framework that was developed was applied to the 230 information products that were catalogued. The results of this assessment can be found in Table 3.1.

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The results of this additional analysis on information products whose main purpose was research priority setting are presented in the original report, but have not been admitted to this thesis chapter.
Assessment of volume of research priority setting per health area

The number of information products per health area was evaluated. When classified according to level 1 health topics as used by the WHO ePub, the distribution of research priority setting at WHO HQ is as in Figure 3.1.

Table 3.1.
Quality assessment framework

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>%</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the main purpose of the information product to set research priorities, research agenda or evaluate R&amp;D gaps?</td>
<td>Yes: 27% 62</td>
<td>No: 73% 168</td>
<td></td>
</tr>
<tr>
<td>What was the scope of the exercise?</td>
<td>Global: 87% 200</td>
<td>Regional: 4% 10</td>
<td>National: 0% 1</td>
</tr>
<tr>
<td></td>
<td>WHO: 7% 15</td>
<td>Global and regional: 0% 1</td>
<td>Global and WHO: 1% 3</td>
</tr>
<tr>
<td>Was it mentioned that the exercise was informed by a priority setting exercise with a different geographical scope, or that it will inform another exercise with a different scope in the future?</td>
<td>Yes: 7% 16</td>
<td>No: 99% 214</td>
<td></td>
</tr>
<tr>
<td>Were stakeholders consulted as part of the research priority setting process?</td>
<td>Yes: 66% 151</td>
<td>No: 29% 66</td>
<td>Not mentioned: 6% 13</td>
</tr>
<tr>
<td>When stakeholders were consulted, how were the priorities set?</td>
<td>Consensus: 8% 127</td>
<td>Ranking (metrics based): 12% 18</td>
<td>Ranking + consensus: 3% 5</td>
</tr>
<tr>
<td></td>
<td>Compiled by the authors of the final document: 5% 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When stakeholders were consulted, was a list of participants provided in the final document?</td>
<td>Yes: 75% 113</td>
<td>No: 25% 38</td>
<td></td>
</tr>
<tr>
<td>Did the information product mention plans for revision of the research priorities, agenda or R&amp;D gaps, or was a timeframe provided for which these were expected to remain relevant, or was a governance structure in place ensuring periodical revision?</td>
<td>Yes: 34% 79</td>
<td>No: 66% 151</td>
<td></td>
</tr>
<tr>
<td>Was the use of criteria mentioned to be part of the process of setting research priorities?</td>
<td>Yes: 10% 22</td>
<td>No: 90% 208</td>
<td></td>
</tr>
<tr>
<td>Was the use of any established tools mentioned to be part of the process of setting research priorities?</td>
<td>Yes: 3% 7 b</td>
<td>No: 97% 223</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

This project should be seen as an initial step towards mapping global health R&D with a view to identifying gaps in research and setting priorities for research, as specified by the Global Strategy and Plan of Action (GSPA) on Public Health, Innovation and Intellectual Property and the WHO strategy on research for health.6,56 Our assessment only included priority setting exercises led by WHO HQ. Although this sample is limited, the scope of research priority setting exercises that were assessed was generally global (i.e. priorities were established to be generically relevant without regional constrictions) and this analysis can therefore be viewed as indicative for global health research priority setting. Secondly, this project analysed methods used for health research priority setting at WHO HQ, assessing and addressing the need for normative work on this issue.

Several conclusions can be drawn from the project. Firstly, the assessment of volume of research priority setting exercises per health area provided results that have a relevance for future identification of global health research priorities. From our analysis a focus on infectious and parasitic diseases became apparent with less priority setting in the areas of

Notes:

a Main purpose was defined as the establishment of research priorities, research agenda or R&D gaps being the primary aim of the information product, or these terms being mentioned in the title of the information product.

b One information product mentioned use of the Combined Approach Matrix (CAM), five information products mentioned use of the Child Health and Nutrition Research Initiative (CHNRI) approach and one information product mentioned use of Delphi techniques.
chronic diseases and conditions and of emergencies. This assessment cannot be taken as a true measure of the global situation, but if there are health areas where research priorities have remained absent on a global level, then to set research priorities for these areas should be a priority. It remains to be decided whether a meta-analysis or review of previous global priority setting exercises would be appropriate as a summary of global health research priorities, or if a specific global exercise needs to be undertaken.

Secondly, this project shows that a wide variety of research priority exercises was undertaken at WHO HQ and that researchers often chose to develop their own, unique methods for setting research priorities, rather than using one of the available tools for research prioritization. A need for more guidance on the topic was often expressed. The contextual differences between individual exercises confirmed that a gold standard or best practice for research priority setting is not appropriate.

ACKNOWLEDGEMENTS

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REFERENCES


A checklist for health research priority setting: nine common themes of good practice

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ABSTRACT
Health research priority setting processes assist researchers and policymakers in effectively targeting research that has the greatest potential public health benefit. Many different approaches to health research prioritization exist, but there is no agreement on what might constitute best practice. Moreover, because of the many different contexts for which priorities can be set, attempting to produce one best practice is in fact not appropriate, as the optimal approach varies per exercise. Therefore, following a literature review and an analysis of health research priority setting exercises that were organized or coordinated by the World Health Organization since 2005, we propose a checklist for health research priority setting that allows for informed choices on different approaches and outlines nine common themes of good practice. It is intended to provide generic assistance for planning health research prioritization processes. The checklist explains what needs to be clarified in order to establish the context for which priorities are set; it reviews available approaches to health research priority setting; it offers discussions on stakeholder participation and information gathering; it sets out options for use of criteria and different methods for deciding upon priorities; and it emphasizes the importance of well-planned implementation, evaluation and transparency.

INTRODUCTION
Setting priorities for health research is essential to maximize the impact of investments, which is especially relevant in resource-poor environments. Health research prioritization is regarded as a key part of efforts needed to strengthen national health research systems.1-6 Additionally, prioritization mechanisms are necessary to facilitate the current demand for increased harmonization of health research at a global level,4,7-10 particularly in combination with analyses of financial flows for health research,9,11,12 and burden of disease studies.13,14 Numerous World Health Assembly resolutions and the 2004 and 2008 Ministerial Summits on Health Research have stressed the need for action on these issues.4,15-19

For health research priority setting exercises to effectively target research with the greatest public health benefit, it is important that they are of high quality and so there is a need for consensus on what constitutes quality or good practice in this area.2,20 The various approaches that are available to guide priority setting for health research differ on important aspects of the process.20-29 Because of the different contexts for which priorities can be set, the optimal approach varies per exercise. Consensus on a gold standard or best practice for health research prioritization thus seems difficult to achieve and is, more importantly, not an appropriate response.30 Therefore, taking the heterogeneous nature of research priority setting exercises into account, while recognizing the need for agreement on appropriate guidance for these exercises, we propose a checklist that outlines options for different approaches and defines nine common themes of good practice for health research prioritization processes. It is intended to provide assistance for planning a high-quality health research priority setting exercise whether at national, regional or global level.

METHODS
Several methodological approaches were combined to acquire a comprehensive overview of common views on good practices in health research priority setting. First, a literature search was conducted of Pubmed for peer-reviewed literature that discussed good practices in health research priority setting (search terms: (setting priorities [title/abstract] OR priority setting [title/abstract]) AND research [title/abstract]). Additionally, the World Health Organization (WHO) library database (WHOLIS) was sought for literature emanating from WHO on this topic (search terms: (research AND priorities) OR (research AND priority) OR (research AND agenda)).31

Secondly, health research priority setting exercises that were organized or coordinated by WHO headquarters since 2005 were reviewed. Documents describing these exercises were identified through the search of WHOLIS and by a manual search of all departmental websites
Nine common themes for good practice in health research priority setting (i.e. elements of a health research priority setting process that are key and should not be overlooked) emerged and were combined into a checklist for health research priority setting (Table 4.1). The nine themes broadly fall into three different categories. Five are especially important in the preparation phase of the prioritization process, two concern methods for deciding upon priorities and two relate to work that is usually performed after priorities have been set.

Preparatory work

1. Context

There are several contextual factors that underpin the process of research priority setting, namely practical considerations about available resources, the focus of the exercise, the values that stakeholders adhere to, and the health, research and political environment in a country. These factors influence the prioritization process and the eventual research priorities and should therefore be discussed explicitly from the beginning of the exercise.21,33

Careful planning of the prioritization exercise is important to establish an exercise that meets the initial expectations. It is necessary to identify available financial, human and time resources.33

A clear focus or scope must be defined for the exercise: What is the exercise about and who is it for?21,12 Factors such as the target disease burden or risk factor (which health research areas does the exercise aim to address), the geographical scope (global, regional, national, sub-national or institutional), the intended timeframe (long-term or short-term priorities), the intended beneficiaries (e.g. children, elderly, urban/rural areas) and the target audience of the research priorities (e.g. policymakers, funding organizations, researchers) must be known before priorities can be set.

The values or principles of an exercise should also be clarified.21,33,34 Should priorities be cost-effective or equitable, or combine both criteria?21 Should there be an emphasis on a particular type of research (e.g. research among children)? Does the nature of the institution setting the priorities influence the values of the exercise? Are there any external demands for the exercise (e.g. political or commercial) that have an influence?21 Diverging principles or values between different stakeholders or disciplines are likely and should be resolved in a fair and legitimate manner.21,34

For country-level exercises scanning the health, research and political environment of the country is of particular importance.26,28 Who has the political power to set priorities? Who has previously set priorities? How do policymakers perceive research for health? What kind of capacity exists to do, use, and fund research?

2. Use of a comprehensive approach

There exist a number of comprehensive approaches to health research priority setting. These approaches are comprehensive because they provide structured, detailed, step-by-step guidance for the entire priority setting process, covering many of the points on this checklist. They assist in the preparatory work of an exercise, in deciding on priorities, and in what to do after priorities have been set. Use of these approaches is therefore in general advantageous and their use should be at least considered. Four commonly used comprehensive approaches are:

- 3D Combined Approach Matrix (CAM) – Focus on the structured collection of information.21,30,31

  The CAM offers a structured framework for the collection of information according to several important criteria for research priority setting and takes into account the influence of different actors and factors.21 Recently, a dimension on equity was added to this framework.21 The process for deciding on priorities is consensus-based. The CAM has been used for both global and national exercises.

- Essential National Health Research (ENHR) approach – Focus on health research priority setting for national-level exercises.21

  The ENHR approach provides guidance for the entire process of setting priorities for health research on a national level. It is a step-by-step manual for facilitators of a national priority setting process.

- The Child Health and Nutrition Research Initiative (CHNRI) approach – Focus on a systematic algorithm for deciding on priorities.22

  The CHNRI approach to research priority setting provides specific guidance for the entire process of setting research priorities. It offers a detailed, systematic algorithm for the identification of research priorities that pools individual scorings of research options based on five weighted criteria. The CHNRI approach has been used for both global and national exercises.

- The Council on Health Research for Development (COHRED) management process to priority setting – Focus on the management process for national-level exercises.26,28

  Recently, COHRED has developed a management approach for countries to set health research priorities. This high-level approach delineates important steps of a priority
A checklist for health research priority setting

**PREPARATORY WORK**

1. **Context**
   Decide which contextual factors underpin the process: What resources are available for the exercise? What is the focus of the exercise (i.e., what is the exercise about and who is it for)? What are the underlying values or principles? What is the health, research and political environment in which the process will take place?

2. **Use of a comprehensive approach**
   Decide if use of a comprehensive approach is appropriate, or if development of own methods is the preferred choice. These approaches provide structured, detailed, step-by-step guidance for health research priority setting processes from beginning to end.

3. **Inclusiveness**
   Decide who should be involved in setting the health research priorities and why. Is there appropriate representation of expertise and balanced gender and regional participation? Have important health sectors and other constituencies been included?

4. **Information gathering**
   Choose what information should be gathered to inform the exercise, such as literature reviews, collection of technical data (e.g., burden of disease or cost-effectiveness data), assessment of broader stakeholder views, reviews or impact analyses of previous priority setting exercises or exercises from other geographical levels.

5. **Planning for implementation**
   Establish plans for translation of the priorities to actual research (via policies and funding) as a priority at the beginning of the process. Who will implement the research priorities? And how?

**DECIDING ON PRIORITIES**

6. **Criteria**
   Select relevant criteria to focus discussion around setting priorities.

7. **Methods for deciding on priorities**
   Choose a method for deciding on priorities. Decide whether to use a consensus-based approach or a metrics-based approach (pooling individual rankings) or a combination.

**AFTER PRIORITIES HAVE BEEN SET**

8. **Evaluation**
   Define when and how evaluation of the established priorities and the priority setting process will take place. Health research priority setting should not be a one-time exercise!

9. **Transparency**
   Write a clear report that discusses the approach used: Who set the priorities? How exactly were the priorities set?

These comprehensive approaches are reviewed and compared in several documents. As part of a workshop on priority setting methodologies in health research convened by WHO’s Cluster on Information, Evidence and Research (IER), its Department for Research Policy and Cooperation (RPC) and the Special Programme for Research and Training in Tropical Diseases (TDR) in 2008, a matrix was developed reviewing three of these approaches in more detail, providing a summary, discussing strengths and weaknesses, and listing applications of each approach (additional file 1).

Adhering to a comprehensive approach will in general improve the quality of an exercise, but it depends entirely on the context of the priority setting exercise in question whether use of such an approach is appropriate, or whether development of own methods is the preferred choice. Approaches can be tailored to match a specific exercise, retaining the advantages of their comprehensive and detailed methodology, while accommodating existing wishes and needs for the exercise.

The list of approaches provided here is not exhaustive. Other forms of guidance are available, for example those that were developed for specific health research priority setting situations, such as for Health Technology Assessments, applied health services research, guideline development, and patient/carer/clinician priority setting partnerships. Additionally, distinct approaches are often recommended for health policy and systems research. Objective approaches to research priority setting without stakeholder consultation and foresight techniques are also used for health research priority setting. Approaches that help set priorities for health interventions and those for prioritizing health research should not be confused.

3. **Inclusiveness**
   Although objective approaches to health research prioritization that are solely based on burden of disease data or cost-effective analyses do exist, most literature on health research priority setting that was found, and the experts that were consulted, considered stakeholder involvement to be an indispensable part of the process of research prioritization. It is thus important to identify which stakeholders need to be involved in the research priority setting exercise, why their opinions need to be sought and what role they should play in the process (e.g., providing opinion, providing evidence or being a part of the group that decides on priorities).
Fair involvement of stakeholders is important. Priority setting exercises should strive for appropriate representation of different expertise and for balanced gender and regional participation. Different sectors and constituencies that could potentially be involved are for example civil society, policymakers, funders/donors, and members of the public. The interdisciplinary nature of public health suggests a role for many different disciplines in setting research priorities, including health researchers and medical practitioners (often several medical professions and health research disciplines have relevant knowledge), economists, sociologists, and many others. For national exercises, tools are available to assist in the mapping of possible stakeholders. A transparent method should be agreed upon to manage potential conflicts of interest in personal, professional and commercial areas.

In principle broad stakeholder involvement (multisectorial and multidisciplinary) is beneficial for the outcomes of a research priority setting exercise for several reasons. Firstly, it minimizes the chances of research options being overlooked. Different groups of stakeholders tend to prioritize research differently. Secondly, participation in the exercise fosters ownership of the established priorities among those involved, thus increasing the chances of implementation of the priorities. Thirdly, broad participation makes priorities correspond to the needs of those that will implement and those that will benefit from the research priorities. As such, the prioritized research will be a better response to societal and policy needs, increasing the overall credibility of the exercise and the potential impact on health and health equity. Finally, broad stakeholder involvement may prevent unnecessary duplication of prioritization efforts and hence wasting of resources.

Lastly, appropriate leadership of the priority setting process needs to be identified. This can for example be in the form of an executive committee or an advisory group that provides overall guidance on the prioritization process, while a larger core working group or decision making group actually decides on priorities. Good leadership can be pivotal in creating and sustaining a high-quality priority setting process.

4. Information gathering

There are many ways to make the priority setting process better informed and choices should be made on which types of information are necessary. These can include the collection of technical data that are often needed to inform discussion on research priorities (see Criteria), such as burden of disease, cost-effectiveness of interventions, current resource flows towards particular research areas, or determinants of disease. Furthermore, in order to be able to prioritize research, one must first know where the gaps in knowledge are; a literature review to identify those gaps is often necessary. Also an initial survey of broader stakeholder views on priorities or opinions on matters related to the research area, or a review or impact analysis of previously established priorities can serve as preparation before the actual exercise.

Research priority setting is needed at different geographical levels: global, regional, national, local within countries, and within organizations. For some health topics, priorities will be the same on all levels. For most, however, priorities will reflect the context they are seeking to address. Research priorities from different levels can be used to inform each other. For global exercises, awareness of national and regional research priorities is important in reaching an inclusive research agenda that is relevant for national and regional contexts. The development of national health research agendas in turn can benefit from awareness of local research priorities, set by primary care teams. Vice versa, global or regional research priority setting exercises can be of value in informing research priority setting on a national level. To facilitate information exchange on national health research agendas in and for low- and middle-income countries, an interactive, web-based information platform on health research called the Health Research Web was recently initiated by COHRED. The platform contains a section aimed at collecting national health research priorities.

Finally, there are many organizations (such as COHRED, CHNRI and the Global Forum for Health Research) that have specialized in providing advice on the process of health research prioritization. Other organizations such as TDR aim to support the identification of health research priorities. Consulting individuals or organizations with previous experience in health research priority setting as part of the preparatory work can aid in obtaining a higher quality process for setting priorities.

5. Planning for implementation

Health research priorities that are set by an organization or country to inform its own funding policies are likely to be linked with implementation strategies. Research priority setting exercises are however often faced with considerable inherent implementation issues because priorities are set by those who are not directly responsible for their implementation. If that is the case, planning for implementation should be a priority during the initial phase of a research priority setting exercise (and not be left till after priorities are established). It is important to decide who the priorities are being set for, and what that target group needs. It should be mapped out in advance which stakeholders are required to be included in the exercise for a feasible and sustainable implementation of the established research priorities. For example, the involvement of policymakers and funding organizations from the beginning means that support for the priorities is more likely and increases the opportunity for research priorities to be translated into actual research. Other examples of facilitation of implementation are classification of priorities into themes, engagement of media in the exercise to increase coverage, adaptation of global research priorities at regional or national level and writing evidence-informed policy briefs. More information on making effective use of health research evidence in policymaking can be found on the website of the WHO Evidence-Informed Policy Network (EVIPNet).
Deciding on priorities

6. Criteria
Criteria are used to focus discussion around research priorities and to ensure that important considerations are not overlooked. They allow for different research dimensions to be balanced against one another depending on the identified values or principles of the exercise, which is reflected in their variation across different exercises and comprehensive approaches to research priority setting.\textsuperscript{21,23,43,51,82–85} Examples of criteria are the magnitude of a health problem, the likelihood of reducing disease burden, cost-effectiveness, the present level of knowledge, current resource flows, the degree of equitability, sustainability, ethical aspects and local research capacity, but there are many more possibilities. Commonly, criteria can be categorized into one of three dimensions: Public health benefit (should we do it?), feasibility (can we do it?) and cost (Figure 4.1). Participants in the priority setting exercise should decide by consensus on appropriate criteria at the beginning of the exercise.

Figure 4.1.
There are three common categories of criteria against which different research options can be considered

![Diagram showing three categories of criteria: Public health benefit, Feasibility, and Cost](image)

7. Methods for deciding on priorities
There are several different methods that can be used to actually decide on priorities. These broadly fall into two groups: consensus based approaches and metrics based approaches. The former lead priorities to be decided by group consensus, the latter involve metrics or an algorithm that results in pooling of individual rankings of research options. Consensus tends to improve the acceptability of the exercise; individual ranking prevents dominance of a few participants. An example of a consensus based approach is the Combined Approach Matrix (CAM).\textsuperscript{21,36,37} Given that all stakeholders are typically not equal and are knowledgeable in different areas, it is especially important for consensus based approaches to take into account diverging values and viewpoints between stakeholders; there are several methods available to do so.\textsuperscript{25} Two examples of metrics based approaches are Delphi-like techniques and the method as employed by CHNRI.\textsuperscript{22,87} Approaches that combine consensus with some form of metrics are common; research options are then first individually prioritized and consequently discussed (or vice versa). This can be an iterative process, as is possible for example in the nominal group approach.\textsuperscript{28}

If one chooses to rank priorities, this also can be achieved in different ways. Ranking can be performed per research option with the criteria as guidance for discussion and thought. Conversely, research options can be ranked per criterion. In the latter case, different criteria can even receive different weights according to their contextual importance.\textsuperscript{22,23} Another option is to differentiate between ranking priority issues and priority research questions. The former could be performed by a broad stakeholder group up front and the latter by technical experts.\textsuperscript{1,40,65} A detailed discussion of different ranking techniques can be found on the COHRED website.\textsuperscript{28}

After priorities have been set

8. Evaluation
The identification of health research priorities should be seen in the broader context of health research coordination and inform funding and policymaking for health research in a sustainable manner. Hence, previously set priorities should be periodically reviewed to ensure that priorities are up to date. Besides updating research priorities, other forms of evaluation can be considered. Evaluation of the process used to set priorities can increase the quality and acceptability of that process.\textsuperscript{25} Furthermore, to make research prioritization legitimate and fair, an appeals mechanism for the established priorities can be considered, providing opportunity for feedback.\textsuperscript{63,90} Finally, performing an impact analysis, for example in the form of a review of research performed and/or funding allocated based on previously established priorities, can be valuable.\textsuperscript{75} Not only can this provide insight into priorities that have remained devoid of attention, but it can also enforce discussion on implementation issues.

9. Transparency
When writing a report of the exercise, being as transparent as possible is crucial. Potential implementers of health research priorities are unlikely to adopt or use priorities unless they are fully informed of all aspects of the priority setting process; transparency increases the credibility and thus the acceptability of the final result. Therefore, the report should not be limited to stating a list of priorities, but should also explain how those priorities were
This lack of guidance has had a negative result on the quality of exercises. Among the exercises we reviewed, often one or more of the elements of good practice we identified here were overlooked.

**DISCUSSION**

It is commonly accepted that health research priority setting processes assist researchers and policymakers in effectively targeting research that has the greatest potential public health benefit.17,33,73 Particularly for low-income countries, national research priorities can facilitate the transformation of a donor-driven research agenda to an agenda driven by countries’ needs.4,50 The establishment of such a nationally owned research agenda is consistent with the Paris Declaration and Accra Agenda for Action, in which country ownership of developmental strategies is regarded a fundamental consideration for the achievement of enhanced aid effectiveness.21

On a global level, research for health has been prioritized comprehensively (i.e. covering all health research areas) on several occasions.6,8-10,13,19,54 Additionally, numerous exercises are continuously being conducted to prioritize health research for specific health areas. Setting priorities for research globally is essential to provide more direction to the currently fragmented global approach to health research funding.17 and to reduce the inequities in allocation of funding towards research commonly articulated as the 10/90 gap.4 There are several groups of health research funders, such as the Heads of International Research Organizations (HIROs) and Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts (ESSENCE), that could bring more harmonization and alignment in funding for global health research. In order to accomplish this, consensus on mechanisms to identify common priorities will be indispensable.7

There are a number of comprehensive approaches to health research priority setting available to guide researchers step by step in setting research priorities. These approaches have been extensively tested and have proven their value. Their detailed methodologies, although varying per approach, all ensure that the priority setting process is comprehensive and complete. However, the review that we performed of health research priority setting exercises that were organized or coordinated by WHO revealed that many researchers choose to develop their own, unique methods.52 Existing needs and contextual particularities of priority setting exercises cannot always be accommodated by one of the existing approaches. For those who wish to develop their own methods to research priority setting, the amount of available aid has been limited to date.20,28,32,33,72,82,83 This lack of guidance has had a negative result on the quality of exercises. Among the exercises we reviewed, often one or more of the elements of good practice we identified here were overlooked.

The checklist helps those seeking to undertake a health research priority setting exercise to make an informed choice as to which comprehensive approach to use or provides assistance for creating a high-quality priority setting process without use of an existing approach. It lists nine common themes for good practice that deserve to be considered in any health research prioritization exercise. This element of consideration (instead of specific guidance) is key throughout the checklist: rather than suggesting a particular path, it has been developed to accommodate the flexibility required by different contexts.

The checklist was tested by informing health research priority setting exercises with a global scope at WHO.71 It is hoped that in the future it will also prove to be of value in informing national-level exercises. Additionally, the generic framework that the checklist offers provides a useful template for future collection of more detailed information on good practices in health research prioritization. In this chapter key references are provided under the respective sections, but this information is not exhaustive. More detailed guidance should be collected and compiled in one place as part of the resources available to support countries in organizing health research, in line with the WHO strategy on research for health and the Global Strategy and Plan of Action (GSPA) on Public Health, Innovation and Intellectual Property.9,16 Work in this area has already been performed by COHRED who have collected a wide range of tools that can aid health research priority setting in national contexts.21

**CONCLUSION**

There are as many approaches to health research prioritization as there are priority setting exercises. One gold standard or best practice is therefore not attainable, nor appropriate. The identification of common themes for good practice fulfills the need for a generic guidance on this variable and intricate process. The checklist for health research priority setting provides practical assistance for the formation of a high-quality priority setting process and can aid researchers and policymakers in effectively targeting health research that is needed the most.

**ADDITIONAL FILES**

Additional file 1: Summary of three commonly used research priority setting methods. This file contains a matrix that was developed as part of a workshop on priority setting methodologies in health research that was convened by WHO’s Cluster on Information, Evidence and Research (IER), its Department for Research Policy and Cooperation (RPC) and the Special Programme for Research and Training in Tropical Diseases (TDR) in 2008. It reviews
three comprehensive approaches in more detail, providing a summary, discussing strengths and weaknesses, and listing applications of each approach. This file was not admitted to this thesis but can be accessed at http://www.health-policy-systems.com/content/8/1/36.

ACKNOWLEDGEMENTS

We would like to thank all who have provided us with comments and suggestions for the checklist through several seminars and expert consultations. We are especially indebted to Dr Catherine d’Arcangues from the Department of Reproductive Health and Research (RHR) of WHO, Dr Joachim Hombach from the WHO Initiative for Vaccine Research (IVR), Dr Emilie van Deventer from the Department of Public Health and Environment (PHE) of WHO, Dr Gabriela Montorzi and Sylvia de Haan from the Council on Health Research for Development (COHRED) and Dr Igor Rudan from the Centre for Population Health Sciences of the University of Edinburgh Medical School and the Croatian Centre for Global Health of the University of Split. Furthermore, we are grateful to Miriam Clados and Julia Fan Li from the Department

A checklist for health research priority setting

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20. Priority Setting Methodologies in Health Research: A workshop convened by WHO’s Cluster on Information, Evidence and Research (IER), its Department for Research Policy and Cooperation (RPC) and the Special Programme for Research and Training in Tropical Diseases (TDR) for reviewing drafts of this manuscript.
A checklist for health research priority setting

76

77


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Aid alignment for global health research: the role of HIROs

Published as
Viergever RF.
Aid alignment for global health research: the role of HIROs.
INTRODUCTION

There is no global coordination of research and development for major diseases, and the global health research and innovation system is highly fragmented. Such was one of the conclusions of the report of the World Health Organization (WHO) Expert Working Group on Research and Development Financing that was finalized in the past year. This conclusion is not novel; it has been consistently argued for decades that the lack of a harmonized approach for prioritizing, funding, and planning research for health has prevented that research from responding adequately to the world’s health needs. To this day, the allocation of health research funding exhibits little tendency to be commensurate with burden of disease, and only a small percentage of funding is allocated towards research that addresses the health problems of developing countries, an issue often referred to as the 10/90 gap. The harmful consequences of this funding gap for everyday clinical practice in developing countries are extensive. For instance, in 2006 it was shown that 30 years of pharmaceutical research had resulted in the development of only 21 drugs targeting neglected diseases (including malaria and tuberculosis) out of a total 1556 new chemical entities marketed. Although the emergence of public-private partnerships, increases in total expenditure on global health research and in the number of actors engaged in that research, and a shift in epidemiology of disease in low- and middle-income countries have all substantially changed the landscape of health research for development in recent years, the enduring mismatch between health research needs and investments remains a cause for grave concern.

DISCUSSION

The Global Ministerial Forum on Research for Health in Bamako in 2008, in line with the Paris Declaration and the Accra Agenda for Action, recognized the need for increased coordination in the field of research for health and the important role of research funding institutions therein. It called on funders of research and innovation ‘to better align, coordinate, and harmonize the global health research architecture and its governance’. There are several collaborative groups of funders of research for health that appear to be well situated to achieve this. One such group is the Heads of International Research Organizations (HIROs). HIROs was established more than ten years ago and brings together government and philanthropic funding institutions for biomedical research, including major funders such as the US National Institutes of Health and the Bill and Melinda Gates Foundation. The enormous collective influence of these organizations is apparent, but is also demonstrated by the impact external donors have been shown to have on WHO’s budget allocations and by research showing that a small group of eleven organizations (many of which are a part of HIROs) currently provide 75% of global funding for neglected disease research and development. Besides HIROs, there are other groups where funders of research for health collaborate. Especially the ‘Enhancing Support for Strengthening the Effectiveness of
National Capacity Efforts’ initiative (ESSENCE) – a collaborative framework between funding agencies to scale up research capacity and increase the effectiveness of research for health in Africa – has recently made some encouraging first steps in aligning donor funding towards national priorities for health research. Other examples are the Product Development Partnership (PDP) Funders group (formerly known as the PDP Donor Coordination Group), whose purpose is to facilitate donors in supporting and monitoring the performance of PDPs, the International Forum of Research Donors (IFORD), which brings together funders of research related to international development, and the International Health Partnership+ (IHP+), which aims to improve the impact of health aid in general.

In discussing the need for increased coordination among funders of research for health, it is important to consider what exactly needs to be coordinated. Recent positive developments among funders include the identification of common approaches to monitoring and evaluation and sharing research data. However, funders have been found to fall short of agreeing on a harmonized agenda for research funding. This finding is worrying, in order to maximize the impact of research investments on health and health equity it is of fundamental importance that funders agree on common health research priorities, both in countries and on the global level, and act on those priorities in a coordinated manner.

Since HIROs brings together the heads of major funders of biomedical research, it appears to be particularly well suited to give rise to the major changes in health research governance that are called for by the Bamako call to action. Unfortunately, HIROs has made little information available on its goals or on how it aims to achieve increased harmonization, alignment and coordination. An internet search reveals only websites noting that a meeting has taken place, and a search on PubMed for ‘Heads of International Research Organisations’ OR ‘Heads of International Research Organizations’ OR ‘Heads of International biomedical Research Organisations’ OR ‘Heads of International biomedical Research Organizations’ OR HIRO[Title/Abstract] OR HIROs[Title/Abstract] returns no relevant results. HIROs is not the only group where funders collaborate that is sparing with information. Recently, IHP+ was criticized for its lack of transparency. Individual funders have also been criticized for not being transparent enough in their operations.

**CONCLUSION**

An initiative like the HIROs group is most welcome in the crowded field of global health research funders. It is surely one of the few groups that could initiate discussion on aid alignment for global health research. Given the enormous potential benefits of more coordination by this group, the contents of its discussions are of great interest to the global health research community. More transparency on HIROs’ intentions for achieving increased coordination and on its current efforts towards addressing the gap between global health research needs and investments would therefore be desirable.

**ACKNOWLEDGEMENTS**

I would like to thank Eric Budgell and Robert Terry for reviewing drafts of this manuscript.
REFERENCES


“Remarkably, our knowledge of what health R&D is being conducted, where it is being conducted, by whom and how, is very limited.”

This thesis

OBJECTIVE 2

To explore how data on currently ongoing health R&D, in particular registered clinical trial data, can inform health research priority setting processes
06

Mapping available health R&D data: what’s there, what’s missing and what role for a Global Observatory

Published as


Mapping available health R&D data: what’s there, what’s missing and what role for a Global Observatory.

INTRODUCTION

In April, 2012, the WHO Consultative Expert Working Group published its report on financing and coordination of research and development (R&D) related to diseases that mainly affect the world’s poorest people living in developing countries.1,2 The report is the latest assessment of potential solutions to the inequity in the distribution of global health research efforts, first described by the Commission on Health Research for Development in 1990 and later referred to as the ‘10/90 Gap’, which indicates that only a small proportion of global health research expenditure is spent on diseases that have a large burden of preventable mortality in low-income and middle-income countries.3

Advances in knowledge and technology have contributed substantially to improvements in health,4,5 but these gains have not been distributed or shared equally, with disparities in life expectancy and burden of disease especially notable between low-income and middle-income countries, and high-income countries.6 Widespread calls for universal health coverage and to address broader determinants of health show the global imperative to eliminate these avoidable disparities.7–10 One crucial contributing factor is the inadequate investment in R&D to address the specific health problems of poor populations.11,12 This well-recognised investment deficit formed the background to the work of the Consultative Expert Working Group and the process that preceded it including an international commission and several year-long multilateral negotiations.3,13–17 The group’s report, which is being discussed by the governing bodies of WHO, recommends a new approach to global health R&D that involves the implementation of three elements focused on meeting the R&D needs of low-income and middle-income countries: guarantee of sustainable financing; coordination of global efforts; and provision of functions to monitor and inform the research processes in the form of a global observatory on health R&D.

A global observatory on health R&D is needed because our understanding of what health R&D is undertaken, and where, by whom, and how, is very scarce, and such knowledge is necessary to improve priority setting and coordination for health R&D, ultimately to ensure that resources are allocated to diseases and regions where they are needed the most. The establishment of a global observatory on health R&D, which is being discussed at WHO, could address the absence of a comprehensive and sustainable mechanism for regular global monitoring of health R&D.

ABSTRACT

The need to align investments in health research and development (R&D) with public health demands is one of the most pressing global public health challenges. We aim to provide a comprehensive description of available data sources, propose a set of indicators for monitoring the global landscape of health R&D, and present a sample of country indicators on research inputs (investments), processes (clinical trials), and outputs (publications), based on data from international databases. Total global investments in health R&D (both public and private sector) in 2009 reached US$240 billion. Of the US$214 billion invested in high-income countries, 60% of health R&D investments came from the business sector, 30% from the public sector, and about 10% from other sources (including private non-profit organisations). Only about 1% of all health R&D investments were allocated to neglected diseases in 2010. Diseases of relevance to high-income countries were investigated in clinical trials seven-to-eight-times more often than were diseases whose burden lies mainly in low-income and middle-income countries. This report confirms that substantial gaps in the global landscape of health R&D remain, especially for and in low-income and middle-income countries. Too few investments are targeted towards the health needs of these countries. Better data are needed to improve priority setting and coordination for health R&D, ultimately to ensure that resources are allocated to diseases and regions where they are needed the most. The establishment of a global observatory on health R&D, which is being discussed at WHO, could address the absence of a comprehensive and sustainable mechanism for regular global monitoring of health R&D.

Advances in knowledge and technology have contributed substantially to improvements in health, but these gains have not been distributed or shared equally, with disparities in life expectancy and burden of disease especially notable between low-income and middle-income countries, and high-income countries. Widespread calls for universal health coverage and to address broader determinants of health show the global imperative to eliminate these avoidable disparities. One crucial contributing factor is the inadequate investment in R&D to address the specific health problems of poor populations. This well-recognised investment deficit formed the background to the work of the Consultative Expert Working Group and the process that preceded it including an international commission and several year-long multilateral negotiations. The group’s report, which is being discussed by the governing bodies of WHO, recommends a new approach to global health R&D that involves the implementation of three elements focused on meeting the R&D needs of low-income and middle-income countries: guarantee of sustainable financing; coordination of global efforts; and provision of functions to monitor and inform the research processes in the form of a global observatory on health R&D.

A global observatory on health R&D is needed because our understanding of what health R&D is undertaken, and where, by whom, and how, is very scarce, and such knowledge is necessary to improve priority setting and coordination for health R&D. In this report, we describe how a global observatory could provide such information. We consider potential data sources for health R&D information; assess data availability and limitations of the available sources; propose a set of potential indicators; and discuss the value that a global observatory would have nationally, regionally, and worldwide.

This article constitutes a collaborative effort by several different researchers. My role in this collaboration was to analyse the registered clinical trial data and to contribute to writing the article.
### METHODS

**Identification of data sources and indicators**

Global and regional sources that present up-to-date information about health R&D on an ongoing basis at regular intervals were identified through searches of publications, grey literature, and websites. One-off data collection efforts and analyses were not included. National data sources representing one individual country and data from funding organisations or programmes were excluded because of comparability issues.

We used the Frascati Manual definition of R&D, which is: ‘Research and experimental development (R&D) comprise creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society, and the use of this stock of knowledge to devise new applications. It covers three activities: basic research, applied research and experimental development.’ We analysed the type of data available to develop a set of indicators that could be used to measure and track the global inputs to health R&D (e.g. funding and human resources), the R&D processes (e.g. clinical trials), the R&D outputs (e.g. publications, patents, and products registered), and the final consequences of these outputs (e.g. health outcomes). Table 6.1 presents the proposed set of indicators, links them to existing data sources, and shows some of the data limitations. The indicators can be used to analyse the R&D landscape at different levels, including a particular area of research or a specific disease.

**Data sources and analyses**

We assessed a subset of the national indicators listed in Table 6.1 by using available data sources, and focused our analysis on R&D expenditure (in 2009—10) related to a country’s wealth, a sample of registered actively recruiting (in August, 2012) clinical trials, and publications indexed by the Web of Science (2002—11).

### Table 6.1. Indicators and sample of information sources

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Description</th>
<th>Source</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investments</td>
<td>Biennial survey, launched in 2006, tracking overall R&amp;D expenditures, R&amp;D personnel and number of researchers reported by non-EU, non-OECD and non-UNESCO Institute for Statistics countries. Utilizes data from OECD and RICYT, in addition to the country questionnaire. Reports totals and health related R&amp;D.</td>
<td>OECD</td>
<td>Limited scope—only certain geographies, conditions, types of research, limited granularity &amp; reporting. Main output is Gross Domestic Expenditure on R&amp;D (GERD) but also includes expenditure by field of science and health and sciences of innovation.</td>
</tr>
<tr>
<td>Inputs</td>
<td>Annual survey tracking overall R&amp;D expenditure, R&amp;D personnel reported by 42 countries of which 34 are member countries. Main output is GERD but also includes expenditure by field of science and health and sciences of innovation.</td>
<td>Exajet</td>
<td>Limited scope—only certain geographies, conditions, types of research, limited granularity &amp; reporting. Main output is Gross Domestic Expenditure on R&amp;D (GERD) but also includes expenditure by field of science and health and sciences of innovation.</td>
</tr>
<tr>
<td>Outputs</td>
<td>Annual survey, started in 1990, tracking overall R&amp;D expenditures, R&amp;D personnel, publications, and patents reported by Portugal, Spain and 29 RICYT countries. Reports totals and health related R&amp;D.</td>
<td>RICYT</td>
<td>Limited scope—only certain geographies, conditions, types of research, limited granularity &amp; reporting. Main output is Gross Domestic Expenditure on R&amp;D (GERD) but also includes expenditure by field of science and health and sciences of innovation.</td>
</tr>
<tr>
<td>Organisations</td>
<td>Annual survey of R&amp;D disbursements for neglected disease R&amp;D started in 2007.</td>
<td>G-Finder</td>
<td>Limited scope—only certain geographies, conditions, types of research, limited granularity &amp; reporting. Main output is Gross Domestic Expenditure on R&amp;D (GERD) but also includes expenditure by field of science and health and sciences of innovation.</td>
</tr>
<tr>
<td>National data sources representing one individual country</td>
<td>International sources as well as national data sources that do not publish exactly the same figures. Countries do not reply to all sections of the questionnaire. Challenging to ensure and incentivize individual country reporting. Data thereby limit the effects that monitoring/tracking of R&amp;D can have in terms of offering policy support to governments and institutions.</td>
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</table>

## Inputs

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Source</th>
<th>Description</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFHR Monitoring Financial Flows: Global studies published 2001 – 2009</td>
<td>Reports collating and analysing expenditure data on health R&amp;D drawing on OECD, UNESCO, RICYT and other sources; alternating annually between global surveys and studies focused on specific diseases or public investments by individual countries.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>African Union/NEPAD: ASTI &amp; AOSTI</td>
<td>The African Science, Technology and Innovation Indicators (ASTII) Initiative is a program within the African Science and Technology Consolidated Plan of Action being coordinated by NEPAD Agency. Participating countries conduct Research and Development (R&amp;D) and Innovation surveys, the outcomes of which are captured in the African Innovation Outlook (AIO). First round of R&amp;D and Innovation surveys with 19 countries have been finalized.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment Action Group reports</td>
<td>Annual survey of Tuberculosis R&amp;D investments started in 2003.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of researchers</th>
<th>Source</th>
<th>Description</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UNESCO Institute for Statistics</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td></td>
<td>OECD/Eurostat</td>
<td>See above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RICYT</td>
<td>See above</td>
<td></td>
</tr>
</tbody>
</table>

## Processes

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Source</th>
<th>Description</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research projects</td>
<td>National databases</td>
<td>Some databases created and used by funders or research institutions as a mechanism to manage their research portfolio.</td>
<td>Limited comparability, Limited scope, No global or international databases. Although global database is not likely to be feasible, agreement on classification may allow for harvesting of data.</td>
</tr>
<tr>
<td>Registered Clinical trials</td>
<td>WHO International Clinical Trials Registry Platform (ICTRP)</td>
<td>The ICTRP provides a single point of access to information on 200,000 clinical trials registered at 19 different national or regional registries around the world. For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.</td>
<td>Not comprehensive - compliance with registration needs to be improved. Stronger enforcement needed. Registration data are uploaded by trial managers leading to variable data quality. Data quality and adherence to standards can be improved.</td>
</tr>
</tbody>
</table>

## Outputs

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Source</th>
<th>Description</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publications</td>
<td>Thomson Reuters and others</td>
<td>Thomson Reuters’ Web of Science covers research published in more than 12,000 scientific journals and conference proceedings and is presently one of the most extensive sources of R&amp;D outputs. There are also other sources.</td>
<td>Broad but not fully comprehensive coverage of the literature. Predominance of publicly funded research. Bias toward reporting of positive results. Lag period between active research and publication. No clear link between publication and inputs (financing).</td>
</tr>
<tr>
<td></td>
<td>Medline and Pubmed</td>
<td>MEDLINE is the U.S. National Library of Medicine® (NLM) premier bibliographic database that contains over 19 million references to journal articles in life sciences with a concentration on biomedicine. PubMed comprises more than 22 million citations for biomedical literature from MEDLINE, life science journals, and online books. PubMed® provides free access to MEDLINE and links to full-text articles when possible.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Virtual Health Library (BIREME)</td>
<td>Open access online source of extensive health-related literature for the Latin American and Caribbean region supported by PAHO WH.O. Integrates a range of bibliographic and other data sources for the health sciences.</td>
<td></td>
</tr>
</tbody>
</table>
Databases created and used by national and regional patent offices.

WIPO PATENTSCOPE
National or regional limitations
Re:Search provides public access to intellectual property for pharma-

Re:Search (WIPO)

WIPO GOLD is a free public resource which provides a one-stop gateway to

WIPO GOLD

Mapping available health R&D data

To measure GERD, data for 192 countries from 2008—10 were extracted from the online database of the United Nations Educational, Scientific and Cultural Organization Institute for Statistics. Data for health R&D were taken from the Organisation for Economic Co-operation and Development and Eurostat databases, which together cover 49 countries and were updated in March, 2012, and with data generally from 2009. Health GERD, like GERD itself, encompasses all R&D in each country as reported by the units doing the work. To calculate percentages of health R&D expenditure funded by business, public, and other sources, some simplifying assumptions were necessary—notably, that all health R&D carried out by industrial firms was financed by business. Another data source reported by R&D funders instead of performers also exists, and would have given somewhat different estimates. The data are mainly derived from national R&D surveys as reported in the annual joint Organisation for Economic Co-operation and Development—Eurostat—United Nations Educational, Scientific and Cultural Organization Institute for Statistics questionnaire. No single category for health R&D exists, and totals need to be generated from expenditure items available for different sectors of the economy. These surveys are based on the methods and definitions of the Frascati Manual.29 Additional health-related R&D expenditure data were found in national R&D surveys and, for some countries, specific estimation approaches were needed (appendix3).

To calculate the total health R&D investments worldwide, data had to be found for countries not reporting to Eurostat or the Organisation for Economic Co-operation and Development. For several of these countries, data were available from United Nations Educational, Scientific and Cultural Organization Institute for Statistics sources on total R&D done in the medical sciences. For countries without such data, health GERD was extrapolated from the average

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29 This appendix was not admitted to this thesis but is available online at http://www.thelancet.com/journals/lancet/article/PDF/0140-6736(13)61046-6/abstract.
The proportion of health R&D of total GERD from the relevant income group of countries, which is a similar approach to that used in previous studies. For countries with no R&D expenditure data, the average proportion of gross domestic product (GDP) for R&D in the relevant income group of countries was used to extrapolate GERD; health GERD was then extrapolated as explained previously. Estimates of GERD for large oil-producing economies were based on the average proportion of GDP invested in R&D in Kuwait and Saudi Arabia, since this group of countries seems to invest less in research than do other countries with similar incomes.

Bibliometric data were commissioned from Thomson Reuters’ Web of Science database and analysed by Thomson Reuters (Evidence). Academic papers for all topics and for applied health research (all categories of clinical medicine and health sciences, but not basic biomedical research, based on journal classification) for 2002—11 were included. Papers were linked to countries by all listed affiliations. Data for the number of ongoing clinical trials were based on a 5% random sample on August 10, 2012, of all interventional, actively recruiting trials from the International Clinical Trials Registry Platform, which is described in detail elsewhere.

### Table 6.2.
List of type III, II and I diseases based on global burden of disease data

<table>
<thead>
<tr>
<th>Type III Diseases</th>
<th>DALYs Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease burden is at least 35 times higher in low-income and middle-income countries than in high-income countries</td>
<td></td>
</tr>
<tr>
<td>Chagas disease</td>
<td>1869</td>
</tr>
<tr>
<td>Trachoma</td>
<td>1358</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>867</td>
</tr>
<tr>
<td>Syphilis</td>
<td>78</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>77</td>
</tr>
<tr>
<td>Measles</td>
<td>67</td>
</tr>
<tr>
<td>Tetanus</td>
<td>56</td>
</tr>
<tr>
<td>Malaria</td>
<td>48</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>36</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>35</td>
</tr>
<tr>
<td>Leprosy</td>
<td>30</td>
</tr>
<tr>
<td>Maternal haemorrhage</td>
<td>29</td>
</tr>
<tr>
<td>Syphilis</td>
<td>16</td>
</tr>
<tr>
<td>Hypertensive disorders of pregnancy</td>
<td>15</td>
</tr>
<tr>
<td>Japanese Encephalitis</td>
<td>14</td>
</tr>
<tr>
<td>Ascariasis</td>
<td>8</td>
</tr>
<tr>
<td>Abortion</td>
<td>8</td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type II Diseases</th>
<th>DALYs Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease burden is 3–35 times higher in low-income and middle-income countries than in high-income countries</td>
<td></td>
</tr>
<tr>
<td>Obstructed labour</td>
<td>3.7</td>
</tr>
<tr>
<td>Trachoma</td>
<td>3.4</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3.4</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>3.0</td>
</tr>
<tr>
<td>Protein energy malnutrition</td>
<td>2.9</td>
</tr>
<tr>
<td>Dengue</td>
<td>2.9</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2.9</td>
</tr>
<tr>
<td>Hookworm disease</td>
<td>2.8</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2.8</td>
</tr>
<tr>
<td>Birth asphyxia and birth trauma</td>
<td>2.6</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>2.5</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>2.5</td>
</tr>
<tr>
<td>Maternal sepsis</td>
<td>1.4</td>
</tr>
<tr>
<td>Cataracts</td>
<td>1.4</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>1.4</td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td>1.3</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1.3</td>
</tr>
<tr>
<td>Iron-deficiency anaemia</td>
<td>1.2</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>1.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type I Diseases</th>
<th>DALYs Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease burden is no more than 3 times higher in low-income and middle-income countries than in high-income countries</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>2.5</td>
</tr>
<tr>
<td>Epilepsy</td>
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</tr>
<tr>
<td>Nephritis and nephrosis</td>
<td>2.4</td>
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<tr>
<td>Glaucoma</td>
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<tr>
<td>Appendicitis</td>
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<td>Schizophrenia</td>
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<tr>
<td>Cervical cancer</td>
<td>1.9</td>
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<tr>
<td>Refractive errors</td>
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</tr>
<tr>
<td>Oesophageal cancer</td>
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<tr>
<td>Hypertensive heart disease</td>
<td>1.8</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.8</td>
</tr>
<tr>
<td>Bipolar affective disorder</td>
<td>1.8</td>
</tr>
<tr>
<td>Benign prostatic hypertrophy</td>
<td>1.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.8</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>1.8</td>
</tr>
</tbody>
</table>
A specific aim was to assess the relevance of R&D related to improving health in low-income and middle-income countries with the categories of disease types first described by the Commission on Macroeconomics and Health: diseases for which the burden lies overwhelmingly or exclusively in low-income countries (type III diseases), diseases for which the main burden lies in low-income countries (type II diseases), or diseases for which the burden is similar in low-income and in wealthier countries (type I diseases). This categorisation has been used most frequently with a focus on neglected tropical diseases as a typical example of type III diseases, as was done when this typology was introduced.

We applied this classification with the 2011 G-FINDER report to extract data for research done in 2010 into 31 neglected diseases, from basic research through to clinical trials. The G-FINDER report presents funding for diseases in US$. Since the data we present for total GERD are in current purchasing power parity-adjusted dollars, for consistency we adjusted the G-FINDER data to account for this factor by using 2010 purchasing power parity values from the World Bank database. We have adhered to the G-FINDER definition of a neglected disease in our assessment of investments.

A specific aim was to assess the relevance of R&D related to improving health in low-income and middle-income countries with the categories of disease types first described by the Commission on Macroeconomics and Health: diseases for which the burden lies overwhelmingly or exclusively in low-income countries (type III diseases), diseases for which the main burden lies in low-income countries (type II diseases), or diseases for which the burden is similar in low-income and in wealthier countries (type I diseases). This categorisation has been used most frequently with a focus on neglected tropical diseases as a typical example of type III diseases, as was done when this typology was introduced. We applied this classification with the 2011 G-FINDER report to extract data for research done in 2010 into 31 neglected diseases, from basic research through to clinical trials. The G-FINDER report presents funding for diseases in US$. Since the data we present for total GERD are in current purchasing power parity-adjusted dollars, for consistency we adjusted the G-FINDER data to account for this factor by using 2010 purchasing power parity values from the World Bank database. We have adhered to the G-FINDER definition of a neglected disease in our assessment of investments.
We developed a new, additional approach to operationalise the categorisation of diseases to type I, II, or III diseases, on the basis of the disorders or diseases presented in the 2004 Global Burden of Diseases report. The number of disability-adjusted life-years caused by each disease was calculated for all low-income and middle-income countries combined per person. The number of disability-adjusted life-years was also calculated for all high-income countries combined per person. A ratio was then calculated for each disease: the number of disability-adjusted life-years per person in low-income and middle-income countries divided by the number per person in high-income countries. These ratios were then ranked from high to low, where a ratio of 1.0 indicates that the disease is found in equal measure in low-and-middle-income countries and high-income countries. From this list, diseases were categorised subjectively with the following ranges of ratios: type I diseases 0.0 to less than 3.0; type II diseases at least 3.0 to less than 35.0; and type III diseases at least 35.0 (Table 6.2). This approach is useful because it allows for the development of indicators that show how much R&D is being done for diseases whose burden lies mainly in low-income and middle-income countries, in high-income countries, or in both, which lies at the heart of the problem of inequities in the global distribution of health R&D. To exemplify this idea, we applied this approach to our analyses of the global distribution of clinical trials. The cutoff points suggested here are not intended to be prescriptive and were chosen to enable categorisation of diseases in a transparent manner. We would suggest that they form the basis for further discussion and refinement of this categorisation.

DATA AVAILABILITY

Substantial information gaps were apparent for all the assessed health R&D indicators, especially for and in low-income and middle-income countries, where disease burden is greatest. The availability of data for countries’ investments—i.e. what they report and how comprehensively and what is available in international databases—in R&D in general and in health R&D varied widely (Table 6.3). Data for health R&D investments were found for only 37% of all countries. Data availability for this indicator was particularly poor for low-income countries, lower-middle-income countries, and upper-middle-income countries (14%, 19%, and 37%, respectively) and was much better for high-income countries (72%). Countries with small populations account for most of the missing data for high-income countries. Since the high-income countries with large populations contribute most financially to R&D in both relative and absolute terms, the proportion of estimated total health R&D investments that had to be extrapolated was low: only 2% (Figure 6.1).

Notes: (A) Total health R&D investments related to GDP per person (2010) in 70 countries. (B) Publicly (government) funded health R&D investments related to GDP per person (2010) in 44 countries. (C) Estimated number of ongoing clinical trials on the International Clinical Trials Registry Platform per million people (2012) related to GDP per person (2010) in 103 countries. (D) Estimated number of ongoing clinical trials on the International Clinical Trials Registry.”
For the other indicators assessed—clinical trials and publications—important information gaps also exist. Although clinical trials registration is now broadly considered an ethical and scientific responsibility, caveats remain in the enforcement of trial registration, mainly in low-income and middle-income countries. The sample we used in Thomson Reuters’ Web of Knowledge database covers 2956 peer-reviewed journals; however, its coverage of national journals in the native language addressing problems of local interest is incomplete, and a linguistic bias exists in access to publication in English language journals for authors from low-income and middle-income countries.

R&D INVESTMENTS

We estimated the global total investment in health R&D (both public and private sector) to be roughly $240 billion purchasing power parity-adjusted dollars in 2009, with 89.5% ($214 billion) coming from high-income countries, 7.9% ($19 billion) from upper-middle-income countries, 2.6% ($6.2 billion) from lower-middle-income countries, and only 0.1% ($0.2 billion) from low-income countries (Table 6.3). The countries contributing the most in absolute terms were the USA ($119 billion), Japan ($18 billion), Germany ($13 billion), and the UK ($12 billion). The countries contributing the most in relative terms as a proportion of GDP were Switzerland (1.16%), Iceland (1.01%), Denmark (0.89%), the USA (0.84%), and Sweden (0.63%). In general, countries’ investments in health research were related to their wealth (GDP per person; Figure 6.2A).

Calculation of disaggregated estimates for health R&D expenditure funded by business, public, and other sources could only be done for a small subset of mainly high-income countries. The countries for which these values could be estimated contributed 90% of all health GERD. In the high-income countries combined, about 60% of health R&D expenditure came from the business sector, 30% from the public sector, and 10% from other sources (including private non-profit organisations). The relative proportions of funding sources vary substantially between countries (Figure 6.3). As is the case for total health R&D investments, publicly funded health R&D largely corresponded to countries’ wealth (Figure 6.2B).
Mapping available health R&D data

Notes: Data are from 2009 unless indicated otherwise. GERD = gross domestic expenditure on research and experimental development. GDP = gross domestic product.

a Indicates data from different years: Slovakia 2010, Russia 2009–10, Australia and South Africa 2008–09, Switzerland, USA, and Chile 2008.

b ‘Other’ encompasses estimated research and development funds received by government, higher education, and private non-profit institutions from higher education (including the institutional funds of private universities), private non-profit organisations, and from abroad.

Figure 6.4.
Health R&D investments and publications as proportion of total

Notes: (A) Health R&D investments as proportion of total R&D investments related to GDP per person (2010) in 70 countries. (B) Proportion of publicly funded health R&D investments related to GDP per person (2010) in 41 countries. (C) Number of publications published in health-related journals in 2002–11 as a proportion of the total number of publications related to GDP per person (2010) in 174 countries (data from Thomson Reuters: Web of Science [Evidence]). (D) Proportion of total R&D investments for health in relation to proportion of total publications in health. R&D = research and development. GDP = gross domestic product. PPP$ = purchasing power parity-adjusted dollars.

Figure 6.5.
Investments in neglected disease R&D

Notes: Data are from 2009 unless indicated otherwise. GERD = gross domestic expenditure on research and experimental development. GDP = gross domestic product.

a Indicates data from different years: Slovakia 2010; Russia 2009–10; Australia and South Africa 2008–09; Switzerland, USA, and Chile 2008.

b ‘Other’ encompasses estimated research and development funds received by government, higher education, and private non-profit institutions from higher education (including the institutional funds of private universities), private non-profit organisations, and from abroad.
CLINICAL TRIALS AND PUBLICATIONS

We assessed the volume of ongoing global clinical trial activity—i.e. the number of actively recruiting trials registered on the International Clinical Trials Registry Platform, and the number of publications in health journals indexed by Web of Science. Denmark, Estonia, Finland, Sweden, and the Netherlands had the highest number of trials per person, whereas Switzerland, Sweden, Denmark, the Netherlands, and Iceland ranked highest for publications per person (Table 6.3). An association was noted between both ongoing trials and the number of publications and a country’s wealth (Figures 6.2C and 6.2E). Similarly, a link was reported between a country’s health R&D investments and both ongoing trials and the number of publications (Figures 6.2D and 6.2F).

Table 6.4.
Distribution of clinical trials in the WHO International Clinical Trials Registry Platform

<table>
<thead>
<tr>
<th>GROUPS OF DISEASES</th>
<th>NON-COMMUNICABLE DISEASES</th>
<th>COMMUNICABLE, MATERNFAL, PERINATAL AND NUTRITIONAL CONDITIONS</th>
<th>INJURIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of trials per million DALY</td>
<td>52.4</td>
<td>7.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Proportion of all trials</td>
<td>87.3%</td>
<td>10.1%</td>
<td>2.6%</td>
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</table>

<table>
<thead>
<tr>
<th>TYPE OF DISEASES</th>
<th>TYPE I DISEASES</th>
<th>TYPE II DISEASES</th>
<th>TYPE III DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of trials per million DALY</td>
<td>45.7</td>
<td>6.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Proportion of all trials</td>
<td>89.0%</td>
<td>91%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COUNTRY OF RECRUITMENT ¹</th>
<th>HIGH-INCOME COUNTRIES</th>
<th>UPPER-MIDDLE-INCOME COUNTRIES</th>
<th>LOWER-MIDDLE-INCOME COUNTRIES</th>
<th>LOW-INCOME COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of trials per million capita</td>
<td>37.2</td>
<td>2.4</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Estimated number of trials per million DALY</td>
<td>292.7</td>
<td>13.4</td>
<td>3.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Proportion of all trials</td>
<td>89.0%</td>
<td>12.3%</td>
<td>4.7%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Notes:
¹ Percentages do not add up to 100% because categories are not mutually exclusive.

Mapping available health R&D data

Notes: (A) Investments in neglected disease R&D in 2010 related to GDP per person (2010) in 38 countries (data from G-FINDER report). (B) Investments in neglected disease research in 2010 related to total public investments in health R&D (2009—10) in 24 countries. (C) Comparison of public investments in total health R&D (dark purple bars, lower x-axis), and in neglected disease R&D (light purple, narrow bars, upper x-axis) in 34 countries. R&D=research and development. GDP=gross domestic product. PPPS=purchasing power parity-adjusted dollars.

Figure 6.6.
Trends in annual publication outputs, 2002—11

Notes: (A) Investments in neglected disease R&D in 2010 related to GDP per person (2010) in 38 countries (data from G-FINDER report). (B) Investments in neglected disease research in 2010 related to total public investments in health R&D (2009—10) in 24 countries. (C) Comparison of public investments in total health R&D (dark purple bars, lower x-axis), and in neglected disease R&D (light purple, narrow bars, upper x-axis) in 34 countries. R&D=research and development. GDP=gross domestic product. PPPS=purchasing power parity-adjusted dollars.

Figure 6.6.
Trends in annual publication outputs, 2002—11

Notes: (A) Trends in annual number of total scientific publications in 2002—11 in different income groups. (B) Trends in health-related publications in 2002—11 in different income groups. Note the break point in the vertical axis on each graph. Data taken from Thomson Reuters: Web of Science (Evidence).
R&D PROFILES
Many of the health R&D indicators were linked to wealth—i.e. the richer the country, the greater their R&D investments, volume of ongoing clinical trials, and number of publications. However, some indicators seemed to be less dependent on country income than others. Although a weak relation was noted between wealth and health R&D investments as a proportion of total R&D investments, with richer countries usually investing relatively more on health research than poorer countries, this proportion varied widely (Figure 6.4A). Similarly, no strong association was reported between a country’s wealth and the proportion of publicly funded health R&D (Figure 6.4B). This finding shows the role of private sector health R&D investments in individual countries (Figure 6.3), notably the pharmaceutical industry, and suggests that variations exist that depend on countries’ industrial structures, on past and present political decisions, and on the priorities of governments and multinational corporations. No clear relation was recorded between a country’s wealth and the proportion of health-related publications as a total of all research publications (Figure 6.4C). Countries seem to have different health R&D profiles: in some countries, health R&D constituted a small proportion of the total R&D investments, but health publications constituted a large share of publications, and vice versa (Figure 6.4D).

RESEARCH TO ADDRESS UNMET NEEDS
Available data and indicators for assessment of countries’ contributions to the health R&D needs of low-income and middle-income countries are scarce. One method to assess this factor is to study countries’ investments in R&D aimed at developing health products for neglected diseases as defined by the G-FINDER report. Global public and philanthropic investments for neglected disease R&D were $2.4 billion purchasing power parity-adjusted dollars in 2010, which is roughly 1% of total global health R&D investments (Table 6.3). Countries’ public investments in neglected disease R&D varied greatly, and no clear association was reported between countries’ wealth or public health R&D investments and the amount of investment in neglected disease R&D, indicating that different countries set different priorities (Figures 6.5A and 6.5B).

The distributions of ongoing clinical trial research and health-related publications are alternative measures to assess what health R&D is being prioritised. We analysed the number of trials relative to the burden of disease. There were more trials for non-communicable diseases than for infectious diseases and injuries, and more trials for type i diseases than for type II and type III diseases — both by a factor of 7-8 when measured in proportion to the burden of disease. Similarly, more trials recruited in high-income countries than in low-income and middle-income countries (Table 6.4). The proportion of health-related publications with authors from high-income countries was 84% in 2011, an 8% decrease compared with 2002 when the proportion was 92%; 18% and 4% for upper-middle-income and lower-middle-income countries—10% and 2% increases from the 2002 values, respectively; and less than 1% for low-income countries, which was similar to the proportion in 2002 (Figure 6.6).

INVESTMENTS COMPARED WITH NORMS
The Consultative Expert Working Group report concluded with recommendations about countries’ investment levels in health R&D. Governments in developing and developed countries were recommended to invest 0.05—0.1% and 0.15—0.2% of GDP on total health R&D, respectively, and at least 0.01% on research on products to meet the specific health needs of developing countries. These targets are roughly in line with the 2% target of governmental health expenditures proposed by the Commission on Health Research for Development and later endorsed by the World Health Assembly.

We compared countries’ public investments to these targets, recognising the caveats regarding the sporadic nature of the available data (Figure 6.5C). Based on available evidence, the data show large variations and many countries do not meet the targets. Several countries are meeting the general recommendation of investing at least 0.15—0.2% of GDP on total health R&D, but many do not. Notable differences also exist between countries’ contributions towards neglected disease R&D when compared with total public health R&D investments.

PERSISTENT R&D GAPS
Global investments in health R&D are increasing and reached $240 billion purchasing power parity-adjusted dollars in 2010, with $26 billion of this amount spent in low-income and middle-income countries. Estimates of the global total of health R&D investments have been reported at intervals from 1986 ($530 billion invested, of which $1.6 billion was devoted to the health problems in low-income and middle-income countries) through to 2005 ($160 billion invested, including $5 billion in low-income and middle-income countries). However, despite this overall growth in health R&D, our findings show a persistent imbalance between R&D investments and needs-based priorities as measured by all R&D indicators (research inputs, processes, and outputs). R&D investments in neglected disease research account for only 1% of overall health R&D investments; proportions of ongoing clinical trials addressing type II and III diseases are low; and the geographical distributions of health R&D investments, clinical trial research, and health research publications are heavily skewed towards high-income countries. Thus, although the nature of the 10/90 gap has changed since the 1990s, the gap itself very much remains.

Governments in developing and developed countries—10% and 2% increases from the 2002 values, respectively; and less than 1% for low-income countries, which was similar to the proportion in 2002 (Figure 6.6).
Since most health research indicators are related to a country’s wealth, economic development might gradually improve the situation and start to rectify inequities. However, investments in health and in health R&D are important drivers and requirements for economic development.11 Investments in health R&D for unmet health needs are necessary to meet the goal of universal health coverage, which poses challenges at three different levels. The first is to achieve universal coverage of existing health interventions;12 which needs improved delivery and investments in health systems and health services research, including the growing area of implementation research.12 The second challenge is to devise ways to treat patients and avert disease burden that are more effective or less costly than available interventions, which necessitates investments in clinical and behavioural research.13 The third challenge is to discover and develop new technologies that address unmet health needs. Balanced investments in these different domains of health research are prerequisites to achieve universal health coverage.

In view of the universality of health, most new knowledge that results from health R&D can be thought of as a shared global public good.13,14 Since existing incentive systems do not generate sufficient R&D to address the needs of low-income and middle-income countries, the public sector needs to play an active part by contributing to R&D that is relevant to the needs of these countries. Given a basic level of capacity, countries also have the potential to benefit extensively from each other’s contributions. Countries’ prioritisation of health R&D over other R&D areas varies widely. We believe that globally agreed norms might be necessary to secure collective action, especially to meet the needs identified by the Consultative Expert Working Group. Investments at comparable levels, with each country contributing to global health R&D, would aid the conceptualisation of health R&D as a collectively shared public good.13,14 Monitoring of countries’ contributions towards health R&D is crucial to ensure that the output is truly a shared public good, and that countries are able to account for their investment strategies.13,14 Furthermore, as our analyses show, although wealth is a predictor for the size of a country’s national health research portfolio, it is not a predetermining factor for the shape of the national health research portfolio. These interesting differences suggest that strategic or policy decisions have been made, and are available to countries to orientate their R&D towards health priorities.

EXISTING INFORMATION GAPS

We have proposed a set of health R&D indicators to allow for better monitoring and analysis of existing priorities and of countries’ performance. A broad set of indicators allows for a triangulation approach, in which different types of information provide different windows of understanding into the R&D landscape. However, several challenges persist in data availability and applicability for collation of such a set of indicators.

Data sources for monitoring of health R&D are collected mainly by regional or other international economic organisations and by national statistics offices. Thus, indicators mostly have an economic investment focus. No international efforts are assessing the R&D landscape from a health sector perspective. The Organisation for Economic Co-operation and Development and Eurostat have the most comprehensive survey to collect national investment data, but many countries do not report the full dataset. Consequently, the estimation of health R&D expenditures for a given year is laborious and imprecise. Preparations are underway to revise the Frascati Manual, and the needs of national health R&D policy makers should be included in the updated framework for international surveys and in the guidelines for health accounts.10

For non-Organisation for Economic Co-operation and Development countries, the available data for R&D investments are sporadic, incomplete, and inconsistent. Our estimates for countries such as Brazil, India, and China are uncertain and are based on data collected several years ago. These countries seem to have increased their investments in health R&D recently, and our estimates should therefore be interpreted with caution. R&D in the Americas is covered by the regular surveys of the Ibero-American and Inter-American Network for Science and Technology Indicators. No regular, comprehensive reports yet exist that detail health-related R&D investments for countries in Africa or Asia. However, R&D and innovation surveys are planned through the African Science, Technology and Innovation Indicators Initiative, and an African Observatory for Science, Technology and Innovation is in development to provide regular reporting.15

More generally, access to all health R&D data sources remains incomplete, particularly in poor countries where the need for such information is the greatest. Capacity to collate and manage these data sources needs to be supported, combined with appropriate incentives to provide the data with a minimum additional burden. Incentives should be created for researchers, research institutions, and research funders to contribute information.

Our proposed set of indicators can be used at the most aggregated level — i.e. total health R&D in a country and its main general sources. However, funding allocation decisions that affect health R&D are made at lower levels — e.g. within a disease area, within one domain of health R&D, and by different public and private sector participants. Thus, the potential for further disaggregation of information is important and needs agreement on a common health R&D classification system. Although efforts are underway to better align these classification systems across countries,15 and new initiatives to map existing classification systems to a common standard are in development,16 no international standards for health R&D classification yet exist.16 Notwithstanding these challenges, accessibility to data for health R&D has increased greatly in recent years. Our analysis was undertaken without new surveys being done, and took advantage of online resources and databases such as the Organisation for Economic Co-
operation and Development and United Nations Educational, Scientific and Cultural Organization Institute for Statistics databases, the International Clinical Trials Registry Platform, and Web of Science. However, these related sources of information are fragmented and need standardised linkages, because all sources of information have their own strengths and weaknesses (Table 6.1). Triangulation—bringing together of several indicators—would allow mitigation of some of these limitations.

A GLOBAL OBSERVATORY ON HEALTH R&D

The creation of a global observatory on health R&D, as recommended by the Consultative Expert Working Group and outlined in a draft resolution for discussion at the 66th World Health Assembly in May, 2013, could address the information gaps. The functions of such an observatory could include monitoring and reporting of financial flows in support of global health needs; integration of information about R&D financial flows with product pipelines and other resources that support innovation and access to medical technologies; provision of information, reports, and analyses to inform policy makers, funders, researchers and benchmark activities and guide R&D priority setting, with a special focus on low-income and middle-income countries and their health needs; creation of a space to convene stakeholders; initiation of collecting, disseminating, and developing good practices, norms, and standards; and provision of support nationally to build capacity in the monitoring, stewardship, governance, and management of health R&D and innovation. Together, these functions would be expected to lead to improved mechanisms for R&D priority setting and decision making, and to greater efficiency in innovation through enhanced transparency on existing R&D efforts. In Europe, Orphanet, funded jointly by the European Commission, the French National Institute of Health and Medical Research, and the French Directorate General for Health, provides a recent example of how a portal with observatory functions can add value to research, diagnosis, product development, and treatment in a defined disease area, such as orphan diseases.

Substantial technical challenges exist in the establishment of such an observatory, and to add value, a global platform of this type requires long-term commitment and sustainable sources of support. Past efforts, such as the Global Forum for Health Research’s monitoring functions, were unsustainable. The development of a global observatory could be approached in a phased manner, and initial research would need to be done to understand user needs (e.g. governments, researchers, research funders, civil society, and the private sector); identify the incentives needed to generate support for the initiative; and analyse how existing initiatives might be complemented, integrated, or scaled up to meet requirements. Assessment of the costs of a global observatory needs more work, but the costs of such work would be modest compared with the potentially beneficial ramifications if R&D coordination is improved.

Any global observatory needs to build on the principle of data harvesting whenever possible, rather than being the primary collector or generator of data. It should collaborate, as appropriate, with the Organisation for Economic Co-operation and Development, Eurostat, or the United Nations Educational, Scientific and Cultural Organization to assess and improve existing survey methodology with respect to the needs of the health sector. As indicated by the scarce data available in poor countries, efforts to improve global monitoring and reporting should also rely on supporting capacity at the country level to manage national health R&D portfolios. Whereas technical support to undertake research is available in research institutes or academic units, far fewer resources are available to support national research governance capacity. Work is being undertaken by the Council on Health Research for Development through Health Research Web to create a platform to allow reporting of a range of data related to health research, including financing, and to support the management of research portfolios. This approach should also be seen in conjunction with efforts by the United Nations Educational, Scientific and Cultural Organization to introduce and improve R&D surveys in low-income countries. The identification of a package of support for countries to develop their own observatories and manage their own R&D programmes could create both the necessary incentives for enhanced reporting of data, and a way for countries to engage in supporting the development of a global observatory.

CONCLUSIONS

The persistent nature of the gap between health R&D needs and the R&D that is presently funded and undertaken calls for managed approaches to the allocation of scarce health research resources. Health R&D funders, both public and private, should be able to access appropriate and accurate information about health R&D inputs, processes, and outputs. To achieve this aim, national, regional, and global monitoring of health R&D must be strengthened. A global observatory on health R&D would be helpful, and could ultimately enable adequate financing for priority areas, aid efficient use and targeting of low resources, and improve investment decisions through avoidance of duplication and improvement in coordination. Increased transparency would enable countries to be accountable for public investments in health R&D and make knowledge more widely available so that researchers can more easily identify research projects that are similar to their own and make incremental improvements to existing research. Recent negotiations at WHO suggest that member states are supportive of a global observatory on health R&D, which is an encouraging development for global health equity and the achievement of universal health coverage. These plans should now be implemented to secure a sustainable solution for regular mapping of health R&D.
ACKNOWLEDGMENTS
J-AR and CÅ were partly funded by the Norwegian Research Council. Analysis undertaken by RFV and Thomson Reuters (Evidence) were funded by WHO. Authors undertook the research under the auspices of their respective organisations. We thank Sloan Sanford (WHO intern) and Ai Koba (WHO) for help with identification of data sources, Colin Mathers (WHO) for assistance with Table 6.2 and global burden of disease data, and Thomson Reuters (Evidence) for providing data and analysis on research publications.

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Use of data from registered clinical trials to identify gaps in health research and development

Published as
Viergever RF, Terry RF, Karam G.
ABSTRACT

Objective
To explore what can be learned about the current composition of the ‘global landscape’ of health research and development (R&D) from data on the World Health Organization’s International Clinical Trials Registry Platform (ICTRP).

Methods
A random 5% sample of the records of clinical trials that were registered as interventional and actively recruiting was taken from the ICTRP database.

Findings
Overall, 2381 records of trials were investigated. Analysis of these records indicated that, for every million disability-adjusted life years (DALYs) caused by communicable, maternal, perinatal and nutritional conditions, by non-communicable diseases, or by injuries, the ICTRP database contained an estimated 7.4, 52.4 and 6.0 trials in which these causes of burden of disease were being investigated, respectively. For every million DALYs in high-income, upper-middle-income, lower-middle-income and low-income countries, an estimated 292.7, 13.4, 3.0 and 0.8 registered trials, respectively, were recruiting in such countries.

Conclusion
The ICTRP constitutes a valuable resource for assessing the global distribution of clinical trials and for informing policy development for health R&D. Populations in lower-income countries receive much less attention, in terms of clinical trial research, than populations in higher-income countries.

INTRODUCTION

More than two decades ago it was shown that only 5% of the world’s resources for health research and development (R&D) were spent on the health problems of developing countries, which then represented 93% of the world’s burden of preventable mortality. The lack of a rational link between the health R&D that was needed and that which was being conducted resulted in the existence of ‘neglected populations’. This mismatch, which still exists, had and has two main causes. First, the distribution of R&D funding has been – and remains – largely determined by market forces rather than by a more equitable system that is based on health needs.

Second, even when funding for health R&D is distributed by philanthropic or governmental donors, many high-burden diseases and priority areas of R&D can remain badly underfunded. This indicates a lack of appropriate mechanisms for the prioritization and coordination of such R&D. To start addressing these problems, a sense of agreement on a common R&D agenda will have to grow among funders of health R&D – something that, to date, has proven difficult to achieve. As a first step towards such a common agenda, the current composition of the ‘global landscape’ of health R&D needs to be explored so that the gaps in this landscape and neglected populations can be identified. If we are to change how we spend our money on health R&D, we first need to know how we are spending it now.

Unfortunately, we know very little about what health R&D is being conducted, where and how it is being conducted, and who is conducting it. Databases of registered clinical trials may offer a new resource for gaining insight into the health R&D ‘landscape’. In the past decade, trial registration has become broadly accepted as an ethical and scientific responsibility. Enforcing regulations, policies and legislation have been crucial to the success of trial registration. There has been relevant national legislation, the editors of many medical journals have made trial registration a prerequisite for the publication of trial results, and a self-regulating pharmaceutical industry has also promoted trial registration. On several continents, many publicly accessible, online registries have been established to allow investigators to register their clinical trials. In 2005, the International Clinical Trials Registry Platform (ICTRP) was established by the World Health Organization (WHO) to create a platform for linking these clinical trial registries and provide a single point of access to information on all clinical trials conducted globally. Over the last 8 years, the ICTRP has grown into a platform that combines data from 15 different clinical trial registries, both national and regional, and offers access to more than 200,000 registered records of clinical trials.

This study was conducted to explore what can be learned from the clinical trial records available on the ICTRP database about the current composition of the ‘global landscape’ of health R&D. We were especially interested in the distribution of trials across different diseases and countries and the identification of any major gaps in the ‘landscape’.

Use of data from registered clinical trials to identify gaps in health R&D
METHODS

Study sample
By using an automated random sampling function that is available as part of the ICTRP’s data management system, we randomly selected from the ICTRP database 5% of all the records for interventional clinical trials that were registered as actively recruiting participants on 10 August 2012. A 5% sample was considered to be sufficient to produce results that could give a general view, but not too large to hamper the manual extraction of relevant data. For trials that were registered in more than one registry, we included only the record with the earliest registration date. 19 We excluded trials that, according to the ICTRP’s records, were only observational in nature.

Data extraction
Registry name, date of registration, age and sex inclusion criteria, target sample size, study design, study type, study phase and the countries of recruitment for each record were downloaded from the ICTRP and imported into an Excel (Microsoft, Redmond, United States of America) database on 10 August 2012. We manually reviewed the health condition or problem studied, the intervention and the primary sponsor by examining the registered record, and we then coded the data as described in the next section.

Data coding and classifications
We coded the health conditions or problems studied in each selected trial according to Table C3 of the Global burden of disease: 2004 update.19 We categorized the countries in which the subjects of trials were recruited as high-, upper-middle-, lower-middle- or low-income according to the World Bank’s groupings, which are based on gross national incomes per capita. 20 We also identified the WHO region to which each country belonged using the current WHO classification of Member States.21 If a trial was recruiting participants in multiple countries that belonged to the same income group or same WHO region, we counted the group or region only once. We divided primary sponsors (i.e. the individual, organization, group or other legal entity that was responsible for initiating, managing and/or financing a trial) into nine categories: collaborative groups of researchers or doctors; contract research organizations; foundations; government institutions; industries; individuals registered as sponsors; research institutes; universities or hospitals; and ‘other’. We then classified trials as having an industrial primary sponsor, a non-industrial primary sponsor (including collaborative groups, foundations, governments, research institutes and universities or hospitals) or another type of sponsor (including individuals registered as primary sponsors, contract research organizations and ‘other’ sponsors). All data were extracted and coded by one author (RFV) and, if ambiguous, discussed with another author (RFT).

Data analysis
For each health condition or problem studied and for each of the categories used for the countries of recruitment, the number of trials detected in the 5% sample was extrapolated to estimate the total number of actively recruiting, interventional trials with the same characteristic that were registered on the ICTRP. The Wilson score interval 22 was used to calculate 95% confidence intervals for each estimate.

Whenever possible, for each health condition or problem studied, we mapped the estimated total number of related trials on the ICTRP against the corresponding burden of disease in disability-adjusted life years (DALYs).19,22 Additionally, we divided the estimated total number of related trials by the corresponding burden of disease in DALYs to give an estimate of the total number of trials per million DALYs for each health condition. Burden-of-disease data were not available for all of the health conditions that were being investigated in the selected trials.22 In addition, the subcauses of injuries were ignored in these calculations because the sources of the injuries were not included in the majority of the records pertaining to injuries. Among the health conditions and problems, we also excluded residual (“other”) categories, several overarching categories (i.e. skin disorders, endocrine disorders and ‘other neoplasms’) and a small number of specific diseases for which uncertainties in the burden-of-disease estimates were large (e.g. chlamydia, gonorrhoea, neonatal infections, polio, all congenital anomalies, all oral diseases and Chagas disease in low-income countries). Trials that recruited participants with malignant neoplasms in general were redistributed proportionally over all of the disease codes for such neoplasms, in a similar approach to that taken by the authors of the Global burden of disease: 2004 update.29

We expressed estimates of the numbers of trials in the ICTRP database that were recruiting in countries in each income group and WHO region as the numbers of trials per capita. For this, we estimated the sizes of the relevant national populations in the year 2012 using the World Bank’s database of health, nutrition and population statistics.25 For each income group and WHO region, we divided the number of trials per capita by the corresponding total burden of disease in DALYs per capita to obtain an estimate of the total number of trials per million DALYs for each category used for the countries of recruitment.

We derived all burden-of-disease data – which were standard DALYs with time discounting and age-weighting – from the most recently published results of WHO’s Global Burden of Disease study.19,22 We used Z-tests 22 to compare the proportions of trials whose primary sponsor was industrial with the corresponding proportions of trials with non-industrial primary sponsors. All of the data analysis was conducted using the Excel software package.
RESULTS
On 10 August 2012, 2381 clinical trials that were registered as interventional and actively recruiting were randomly selected from the ICTRP database (Figure 7.1). Baseline information on registry name, intervention type, year of registration, sponsorship, target sample size, study phase and inclusion criteria for sex and age of participants is presented in Table 7.1.

Health conditions or problems studied
The health condition or problem studied could be classified for 2195 of the 2381 selected trials. The most common focus of investigation – both in terms of the absolute number of trials and the number of trials per million DALYs caused by the condition or problem – was on non-communicable diseases, followed first by communicable, maternal, perinatal and nutritional conditions and then by injuries (Table 7.2 and Figure 7.2). The estimated total number of trials registered on the ICTRP for each health condition or problem was mapped against the global burden of the condition or problem (Figure 7.3).

Countries of recruitment and sponsorship
Information on countries of recruitment was available for 2377 of the 2381 selected trials. Trials were found to recruit most often in high-income countries – absolutely, per capita and proportionally to the burden of disease in these countries – followed first by upper-middle-income countries, then by lower-middle-income countries and finally by low-income countries (Table 7.3 and Figure 7.4). Trials recruited most often in WHO’s European Region and Region of the Americas (Table 7.3 and Figure 7.5).

We were able to determine country of recruitment and classify the primary sponsor as non-industrial or industrial for 2253 of the 2381 selected trials. Trials with non-industrial primary sponsors recruited more often in low-income countries than trials with industrial primary sponsors (odds ratio, OR: ∞; Z = 2.0; P = 0.0464), whereas trials with industrial primary sponsors recruited more often in upper-middle-income (OR: 4.0; Z = 7.2; P < 0.0001), upper-middle-income (OR: 2.0; Z = 5.0; P < 0.0001) and high-income countries (OR: 2.2; Z = 4.0; P = 0.0001) (Table 7.4). Trials with industrial primary sponsors were more likely to have multi-country recruitment [222 (44.8%) of 495] than trials with non-industrial primary sponsors [73 (4.1%) of 1758] (OR: 18.8; Z = 23.7; P < 0.0001).

Table 7.1.
Baseline information on a 5% sample of trials from the International Clinical Trials Registry Platform, 2012

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SELECTED TRIALS (TOTAL N = 2381)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registry name</td>
<td>N</td>
</tr>
<tr>
<td>CT.gov</td>
<td>1316</td>
</tr>
<tr>
<td>EU-CTR</td>
<td>540</td>
</tr>
<tr>
<td>JPRN</td>
<td>208</td>
</tr>
<tr>
<td>ANZCTR</td>
<td>95</td>
</tr>
<tr>
<td>ISRCTN</td>
<td>61</td>
</tr>
<tr>
<td>ChCTR</td>
<td>43</td>
</tr>
<tr>
<td>CTRN</td>
<td>36</td>
</tr>
<tr>
<td>NCTR</td>
<td>31</td>
</tr>
<tr>
<td>IRCT</td>
<td>23</td>
</tr>
<tr>
<td>DRKS</td>
<td>16</td>
</tr>
<tr>
<td>CRIS</td>
<td>9</td>
</tr>
<tr>
<td>ReBec</td>
<td>2</td>
</tr>
<tr>
<td>PACTR</td>
<td>1</td>
</tr>
<tr>
<td>SPPEC</td>
<td>0</td>
</tr>
<tr>
<td>SLCTR</td>
<td>0</td>
</tr>
<tr>
<td>Intervention type</td>
<td>N</td>
</tr>
<tr>
<td>Drugs and biologicals</td>
<td>1562</td>
</tr>
<tr>
<td>Surgery and other procedures</td>
<td>281</td>
</tr>
<tr>
<td>Behavioural</td>
<td>168</td>
</tr>
<tr>
<td>Device</td>
<td>167</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>119</td>
</tr>
<tr>
<td>Dietary supplements and diets</td>
<td>106</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>64</td>
</tr>
<tr>
<td>Radiation</td>
<td>48</td>
</tr>
<tr>
<td>Organizational</td>
<td>43</td>
</tr>
<tr>
<td>Other</td>
<td>35</td>
</tr>
<tr>
<td>Year of registration</td>
<td>N</td>
</tr>
<tr>
<td>Before 2005</td>
<td>26</td>
</tr>
<tr>
<td>2005</td>
<td>127</td>
</tr>
<tr>
<td>2006</td>
<td>106</td>
</tr>
<tr>
<td>2007</td>
<td>158</td>
</tr>
<tr>
<td>2008</td>
<td>245</td>
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<td>2009</td>
<td>351</td>
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<td>2010</td>
<td>462</td>
</tr>
<tr>
<td>2011</td>
<td>544</td>
</tr>
<tr>
<td>2012</td>
<td>362</td>
</tr>
</tbody>
</table>
Use of data from registered clinical trials to identify gaps in health R&D

### Table

<table>
<thead>
<tr>
<th>Category</th>
<th>Selected trials (Total N = 2381)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td><strong>Primary sponsor</strong></td>
<td></td>
</tr>
<tr>
<td>University or hospital</td>
<td>1459</td>
</tr>
<tr>
<td>Industry</td>
<td>495</td>
</tr>
<tr>
<td>Collaborative group of doctors or researchers</td>
<td>112</td>
</tr>
<tr>
<td>Government institution</td>
<td>99</td>
</tr>
<tr>
<td>Individual</td>
<td>97</td>
</tr>
<tr>
<td>Research institute</td>
<td>51</td>
</tr>
<tr>
<td>Contract research organization</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Not specified or not classifiable</td>
<td>22</td>
</tr>
<tr>
<td><strong>Target number of participants</strong></td>
<td></td>
</tr>
<tr>
<td>1–99</td>
<td>1184</td>
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<tr>
<td>100–999</td>
<td>832</td>
</tr>
<tr>
<td>≥ 1000</td>
<td>94</td>
</tr>
<tr>
<td>Not specified</td>
<td>271</td>
</tr>
<tr>
<td><strong>Study phase(s)</strong></td>
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</tr>
<tr>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>I</td>
<td>166</td>
</tr>
<tr>
<td>I/II</td>
<td>86</td>
</tr>
<tr>
<td>II</td>
<td>432</td>
</tr>
<tr>
<td>II/III</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>265</td>
</tr>
<tr>
<td>III/IV</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>230</td>
</tr>
<tr>
<td>Not specified</td>
<td>1146</td>
</tr>
<tr>
<td><strong>Sex of participants</strong></td>
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</tr>
<tr>
<td>Both</td>
<td>2028</td>
</tr>
<tr>
<td>Female</td>
<td>257</td>
</tr>
<tr>
<td>Male</td>
<td>96</td>
</tr>
<tr>
<td><strong>Age of participants</strong></td>
<td></td>
</tr>
<tr>
<td>0–27 days</td>
<td>76</td>
</tr>
<tr>
<td>28 days–2 years</td>
<td>111</td>
</tr>
<tr>
<td>2–11 years</td>
<td>200</td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>247</td>
</tr>
<tr>
<td>12–17 years</td>
<td>280</td>
</tr>
<tr>
<td>&lt; 18 years</td>
<td>372</td>
</tr>
<tr>
<td>18–64 years</td>
<td>2034</td>
</tr>
<tr>
<td>≥65 years</td>
<td>1582</td>
</tr>
<tr>
<td>Not specified</td>
<td>127</td>
</tr>
</tbody>
</table>

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**Notes:** ANZCTR, Australian New Zealand Clinical Trials Registry; ChiCTR, Chinese Clinical Trial Register; CRIS, Clinical Research Information Service of the Republic of Korea; CT.gov, ClinicalTrials.gov; CTRI, Clinical Trials Registry – India; DRKS, German Clinical Trials Register; EU-CTR, EU Clinical Trials Register; IRCT, Iranian Registry of Clinical Trials; GCRTN, International Standard Randomized Controlled Trial Number Register; JPRN, Japan Primary Registries Network; NTR, Netherlands National Trial Register; PACTR, Pan African Clinical Trial Registry; ReBec, Brazilian Clinical Trials Registry; RPCEC, Cuban Public Registry of Clinical Trials; SLCTR, Sri Lanka Clinical Trials Registry.

* As some of the classifications within this category overlap, some trials are included in more than one classification.

b ‘Other procedures’ included acupuncture and cell transplants.

c For example, psychotherapy and lifestyle counselling.

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**Figure 7.1.**
Flowchart of the sampling of the records of interventional and actively recruiting trials in the International Clinical Trials Registry Platform (ICTRP), 2012
Use of data from registered clinical trials to identify gaps in health R&D

| Table 7.2. | The health problems being investigated in the actively recruiting, interventional trials registered on the International Clinical Trials Registry Platform (ICTRP), 2012 | Pages 130-133 |

<table>
<thead>
<tr>
<th>Health condition or problem</th>
<th>Number of trials in sample</th>
<th>Percentage of trials on the ICTRP</th>
<th>Estimate and (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicable, maternal, perinatal and nutritional</td>
<td>222</td>
<td>10.1 (8.9–11.4)</td>
<td>4440 (3916–5025)</td>
</tr>
<tr>
<td>Infectious and parasitic diseases</td>
<td>132</td>
<td>6.0 (5.1–7.1)</td>
<td>2640 (2236–3111)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>11</td>
<td>0.5 (0.3–0.9)</td>
<td>220 (123–393)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>32</td>
<td>1.5 (1.0–2.1)</td>
<td>640 (454–908)</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>10</td>
<td>0.5 (0.2–0.8)</td>
<td>200 (109–367)</td>
</tr>
<tr>
<td>Childhood cluster diseases</td>
<td>6</td>
<td>0.3 (0.1–0.6)</td>
<td>120 (55–261)</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>1</td>
<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>1</td>
<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
</tr>
<tr>
<td>Measles</td>
<td>2</td>
<td>0.1 (0.0–0.3)</td>
<td>40 (11–146)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>2</td>
<td>0.1 (0.0–0.3)</td>
<td>40 (11–146)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>3</td>
<td>0.1 (0.0–0.4)</td>
<td>60 (20–176)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>8</td>
<td>0.4 (0.2–0.7)</td>
<td>160 (81–315)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>16</td>
<td>0.7 (0.4–1.2)</td>
<td>320 (197–518)</td>
</tr>
<tr>
<td>Malaria</td>
<td>9</td>
<td>0.4 (0.2–0.8)</td>
<td>180 (95–341)</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>2</td>
<td>0.1 (0.0–0.3)</td>
<td>40 (11–146)</td>
</tr>
<tr>
<td>Dengue</td>
<td>2</td>
<td>0.1 (0.0–0.3)</td>
<td>40 (11–146)</td>
</tr>
<tr>
<td>Intestinal nematode infections</td>
<td>1</td>
<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
</tr>
<tr>
<td>Ascariasis</td>
<td>1</td>
<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
</tr>
<tr>
<td>Other infectious disease</td>
<td>32</td>
<td>1.5 (1.0–2.1)</td>
<td>640 (454–908)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>26</td>
<td>1.2 (0.8–1.7)</td>
<td>520 (355–759)</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>16</td>
<td>0.7 (0.4–1.2)</td>
<td>320 (197–518)</td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td>9</td>
<td>0.4 (0.2–0.8)</td>
<td>180 (95–341)</td>
</tr>
<tr>
<td>Otitis media</td>
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<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
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<tr>
<td>Maternal conditions</td>
<td>36</td>
<td>1.6 (1.2–2.3)</td>
<td>720 (521–993)</td>
</tr>
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<td>Maternal haemorrhage</td>
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<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
</tr>
<tr>
<td>Hypertensive disorders of pregnancy</td>
<td>5</td>
<td>0.2 (0.1–0.5)</td>
<td>100 (43–234)</td>
</tr>
<tr>
<td>Obstructed labour</td>
<td>6</td>
<td>0.3 (0.1–0.6)</td>
<td>120 (55–261)</td>
</tr>
<tr>
<td>Abortion</td>
<td>5</td>
<td>0.2 (0.1–0.5)</td>
<td>100 (43–234)</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>0.9 (0.6–1.3)</td>
<td>380 (244–592)</td>
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</table>
### Use of data from registered clinical trials to identify gaps in health R&D

<table>
<thead>
<tr>
<th>Health condition or problem</th>
<th>Number of trials in sample</th>
<th>Percentage of trials on the ICTRP</th>
<th>Estimate and (95% CI)</th>
<th>Number of trials on the ICTRP</th>
<th>Estimate and (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>Per 1 000 000 DALYs</td>
<td>Total</td>
<td>Per 1 000 000 DALYs</td>
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<tr>
<td>Other neoplasms&lt;sup&gt;1&lt;/sup&gt;</td>
<td>25</td>
<td>1.1 (0.8–1.7)</td>
<td>500 (339–736)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>85</td>
<td>3.9 (3.1–4.8)</td>
<td>1700 (1380–2091)</td>
<td>86.3 (70.0–106.1)</td>
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<tr>
<td>Endocrine disorders&lt;sup&gt;2&lt;/sup&gt;</td>
<td>122</td>
<td>5.6 (4.7–6.6)</td>
<td>2440 (2052–2896)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unipolar depressive disorders</td>
<td>28</td>
<td>1.3 (0.9–1.8)</td>
<td>560 (388–807)</td>
<td>8.6 (5.9–12.3)</td>
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<td>Bipolar affective disorder</td>
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<td>0.4 (0.2–0.7)</td>
<td>160 (81–315)</td>
<td>11.1 (5.6–21.8)</td>
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<td>Schizophrenia</td>
<td>26</td>
<td>1.2 (0.8–1.7)</td>
<td>520 (355–759)</td>
<td>31.0 (21.2–45.3)</td>
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<td>Epilepsy</td>
<td>11</td>
<td>0.5 (0.3–0.9)</td>
<td>220 (123–393)</td>
<td>28.0 (15.7–50.0)</td>
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<tr>
<td>Alcohol use disorders</td>
<td>9</td>
<td>0.4 (0.2–0.8)</td>
<td>180 (95–341)</td>
<td>7.6 (4.0–14.4)</td>
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</tr>
<tr>
<td>Alzheimer and other dementia</td>
<td>18</td>
<td>0.8 (0.5–1.3)</td>
<td>360 (228–567)</td>
<td>32.3 (20.4–50.9)</td>
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<tr>
<td>Parkinson disease</td>
<td>11</td>
<td>0.5 (0.3–0.9)</td>
<td>220 (123–393)</td>
<td>128.6 (71.9–229.8)</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>18</td>
<td>0.8 (0.5–1.3)</td>
<td>360 (228–567)</td>
<td>235.7 (149.3–371.6)</td>
<td></td>
</tr>
<tr>
<td>Drug use disorders</td>
<td>16</td>
<td>0.7 (0.4–1.2)</td>
<td>320 (197–518)</td>
<td>38.2 (23.6–61.9)</td>
<td></td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>9</td>
<td>0.4 (0.2–0.8)</td>
<td>180 (95–341)</td>
<td>51.9 (27.3–98.4)</td>
<td></td>
</tr>
<tr>
<td>Obsessive–compulsive disorder</td>
<td>5</td>
<td>0.2 (0.1–0.5)</td>
<td>100 (45–234)</td>
<td>196.0 (84–458)</td>
<td></td>
</tr>
<tr>
<td>Panic disorder</td>
<td>1</td>
<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
<td>2.9 (0.5–16.2)</td>
<td></td>
</tr>
<tr>
<td>Insomnia (primary&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>5</td>
<td>0.2 (0.1–0.5)</td>
<td>100 (45–234)</td>
<td>276.8 (118–645)</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>6</td>
<td>0.3 (0.1–0.6)</td>
<td>120 (55–261)</td>
<td>15.5 (7–33.6)</td>
<td></td>
</tr>
<tr>
<td>Other&lt;sup&gt;3&lt;/sup&gt;</td>
<td>112</td>
<td>5.1 (4.2–6.1)</td>
<td>2220 (1851–2658)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sense organ diseases</td>
<td></td>
<td>3.3 (2.7–4.2)</td>
<td>1460 (1165–1827)</td>
<td>16.8 (13.4–21.0)</td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>12</td>
<td>0.5 (0.3–1.0)</td>
<td>240 (137–418)</td>
<td>50.8 (29.1–88.5)</td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>6</td>
<td>0.3 (0.1–0.6)</td>
<td>120 (55–261)</td>
<td>6.8 (3.1–14.7)</td>
<td></td>
</tr>
<tr>
<td>Refractive errors</td>
<td>4</td>
<td>0.2 (0.1–0.5)</td>
<td>80 (31–205)</td>
<td>2.9 (1.7–7.4)</td>
<td></td>
</tr>
<tr>
<td>Hearing loss (adult onset)</td>
<td>1</td>
<td>0.0 (0.0–0.3)</td>
<td>20 (4–113)</td>
<td>0.7 (0.1–4.1)</td>
<td></td>
</tr>
<tr>
<td>Macular degeneration and other</td>
<td>50</td>
<td>2.3 (1.7–3.0)</td>
<td>1000 (760–1313)</td>
<td>107.6 (81.8–141.2)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>219</td>
<td>10.0 (8.8–11.3)</td>
<td>4380 (3860–4961)</td>
<td>28.9 (25.5–32.8)</td>
<td></td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>5</td>
<td>0.2 (0.1–0.5)</td>
<td>100 (43–234)</td>
<td>19.3 (8.2–45.0)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>28</td>
<td>1.3 (0.9–1.8)</td>
<td>560 (388–807)</td>
<td>69.8 (48.4–100.8)</td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>70</td>
<td>3.2 (2.5–4.0)</td>
<td>1400 (1111–1760)</td>
<td>22.4 (17.8–28.1)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>40</td>
<td>1.8 (1.3–2.5)</td>
<td>800 (589–1065)</td>
<td>172.2 (126.2–233.5)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory heart disease</td>
<td>2</td>
<td>0.1 (0.0–0.3)</td>
<td>40 (11–146)</td>
<td>6.4 (1.8–23.3)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: CI, confidence interval; DALY, disability-adjusted life year; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome.
Use of data from registered clinical trials to identify gaps in health R&D

When summed, the percentages shown for income groups or regions exceed 100% because some trials were recruiting in multiple countries belonging to more than one income group or region.

Table 7.3.
Areas of recruitment for the actively recruiting, interventional trials registered in the International Clinical Trials Registry Platform (ICTRP), 2012

<table>
<thead>
<tr>
<th>Area of Recruitment</th>
<th>Number of Trials in Sample</th>
<th>Estimate and (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of trials on the ICTRP</td>
<td>Total</td>
</tr>
<tr>
<td>World Bank income group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-income country</td>
<td>2115</td>
<td>89.0 (87.7–90.2)</td>
</tr>
<tr>
<td>Upper-middle-income country</td>
<td>292</td>
<td>12.3 (11.0–13.7)</td>
</tr>
<tr>
<td>Lower-middle-income country</td>
<td>111</td>
<td>4.7 (3.9–5.6)</td>
</tr>
<tr>
<td>Low-income country</td>
<td>14</td>
<td>0.6 (0.4–1.0)</td>
</tr>
<tr>
<td>WHO region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>50</td>
<td>2.1 (1.6–2.8)</td>
</tr>
<tr>
<td>Americas</td>
<td>840</td>
<td>35.3 (33.4–37.3)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>65</td>
<td>2.7 (2.2–3.3)</td>
</tr>
<tr>
<td>Europe</td>
<td>1055</td>
<td>44.4 (42.4–46.4)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>96</td>
<td>4.0 (3.3–4.9)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>548</td>
<td>23.1 (21.4–24.8)</td>
</tr>
</tbody>
</table>

Notes: CI, confidence interval; DALY, disability-adjusted life year; WHO, World Health Organization.

- Estimated percentages and numbers for the whole ICTRP were based on the results of the analysis of the records for a 5% sample of the trials registered on the platform.
- The percentages shown are those of the 2195 trials in the sample for which the health condition or problem studied could be classified. The condition or problem investigated in the other 186 trials included in the sample could not be classified because there was insufficient information in the registered records of the trial or because the trials included participants with many different diseases.
- Burden-of-disease data for this condition or problem were either not available or excluded from this table for the reasons given in the Methods section.

Figure 7.2.
Health problems being investigated by trials registered in the International Clinical Trials Registry Platform (ICTRP), 2012

Notes: Only interventional and actively recruiting trials were investigated. The health problems are split according to both the estimated numbers of trials on the ICTRP (top chart) and the global burden of disease that they cause (bottom chart). Confidence intervals were calculated for the estimates but have been omitted from the figure, for clarity. DALY, disability-adjusted life year.
Figure 7.3.
Estimated number of trials in the International Clinical Trials Registry Platform investigating a specific health problem and the burden of disease posed by that problem, 2012.

Notes: Only interventional and actively recruiting trials were included in the analysis. Only trials investigating specific health problems were included in this figure; overarching categories and subcategories of health problems were excluded. Confidence intervals were calculated for the estimates but have been omitted from the figure, for clarity. DALY, disability-adjusted life year; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome.

Figure 7.4.
Estimated numbers of trials in the International Clinical Trials Registry Platform recruiting in low-, lower-middle-, upper-middle- and high-income countries, 2012.

Notes: Only interventional and actively recruiting trials were included in the analysis. For illustration, the burdens of disease in countries in the same income groups are also presented. The error bars on the estimates of trial numbers indicate 95% confidence intervals. DALY, disability-adjusted life year.
DISCUSSION

The global monitoring of health R&D requires analyses of the inputs (e.g. investments\(^{2,5,6}\)), processes (e.g. analyses of the R&D ‘pipeline’\(^{24,25}\)) and outputs (e.g. publications\(^{26}\) or products such as medicines\(^{4}\)) of R&D. Such ‘triangulation’ of different sources of information is essential if we are to obtain a complete picture of what health R&D are being conducted, where and how it is being conducted, and who is conducting it. The increasing public availability of information on clinical trials provides an additional source of information for analysing current processes in health R&D at the global, regional or country levels. Evaluations of registered trial data have recently been used to shed light on national clinical trial portfolios\(^{27, 28}\) and specific research areas\(^{29–32}\). This type of evaluation has several strengths: all trials should be registered, even if their final results are never published; registered records generally contain information that is additional and complementary to that in any published articles on the trials;\(^{29}\) databases of registered trials can provide insight into currently ongoing R&D; and their standardized and searchable format makes databases of registered trials suitable for aggregate analysis.\(^{34}\) For the purpose of obtaining a comprehensive global picture of all ongoing clinical trials, the ICTRP is an unmatched resource of information since it provides access to data from all of the major clinical trial registries around the world that meet the relevant standards of WHO’s registry criteria.\(^{35}\)

Table 7.4.
Types of primary sponsor for a 5% sample of trials from the International Clinical Trials Registry Platform, 2012

<table>
<thead>
<tr>
<th>Area of Recruitment (^a)</th>
<th>Trials with Non-Industrial Sponsor N (%)</th>
<th>Trials with Industrial Sponsor N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-income country</td>
<td>1550 (88.0)</td>
<td>467 (94.3)</td>
</tr>
<tr>
<td>Upper-middle-income country</td>
<td>183 (10.4)</td>
<td>93 (18.8)</td>
</tr>
<tr>
<td>Lower-middle-income country</td>
<td>49 (2.8)</td>
<td>51 (10.3)</td>
</tr>
<tr>
<td>Low-income country</td>
<td>14 (0.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>All</td>
<td>1758 (100)</td>
<td>495 (100)</td>
</tr>
</tbody>
</table>

Notes:
- \(^a\) Categorized according to the World Bank income groupings.\(^{20}\) When summed, the percentages shown for income groups or regions exceed 100% because some trials were recruiting in multiple countries belonging to more than one income group.

Figure 7.5.
Estimated numbers of trials in the International Clinical Trials Registry Platform recruiting in each of WHO’s regions, 2012

The results of this study show that, at least on a global scale, there is little correlation between the burden of disease attributable to a particular health condition or problem and the amount of clinical trial research being conducted on that health problem. This finding confirms the mismatch – between health R&D need and relevant health R&D – that has previously been observed using alternative R&D metrics, such as R&D investments and R&D outputs.\(^{1–4,6,31,36}\) A consequence of this mismatch is the existence of several populations that are neglected with respect to health R&D.\(^{3}\) In particular, health R&D currently does not adequately meet the needs of populations in lower-income countries.\(^{3,37}\) In general, communicable, maternal, perinatal and nutritional conditions – which cause a much higher proportion of the burden of disease in lower-income countries than in high-income countries\(^{19}\) – currently receive much less attention, in terms of clinical trial research, than non-communicable diseases. In addition, clinical trials recruit much less often in lower-income countries than in higher-income countries. For health conditions or problems that cause a large burden in both lower- and higher-income countries, it is important that populations in lower-income countries be included in clinical trial research so that their specific R&D needs can be addressed.\(^3\)
There are several limitations in using registered trial data for identifying gaps in the health R&D ‘landscape’. To begin with, no account is taken of research other than that conducted within the context of a clinical trial. Since a registry for systematic reviews has recently been established and the creation of a registry for observational research has been widely advocated, evaluations of the health R&D ‘landscape’ may soon broaden in scope. Another potential data source could be a registry (or database) of research protocols or even raw datasets, although the information in such a registry would be much more difficult to analyse than the registered records of clinical trials.

The need for clinical trial research on a given health problem – or the perceived need for such research – is only partly determined by the burden of disease posed by the problem. The severity of the corresponding product shortfall, the state of the relevant science and such research – is only partly determined by the burden of disease posed by the problem. The main strength of the findings of the present study lies in the general, global trends that the findings reveal. For more specific conclusions about individual diseases, registered trial data will have to be analysed alongside other sources of information.

To date, very little reliable information has been produced on how much clinical trial research is being conducted in lower-income countries. Although the present results help to fill this knowledge gap, it is important to note that the registration of trials has not been enforced equally around the world. Many countries still have no legislation to ensure registration and not all journals in which clinical trial data could be published are covered by the journal associations that have committed to enforcing trial registration. Furthermore, not all clinical trials are conducted with the goal of publication. It is difficult to verify or even estimate how many clinical trials remain unregistered, although it seems likely that at least some trials are never registered, especially in countries where there is no legal requirement for registration. Given that all major medical journals now require evidence of trial registration, as a condition for publication of any data from a trial, and that all studies that assess the effects of new medicines – for which regulatory approval is to be sought internationally – need to be registered, the quality and potential impact of any unregistered trials are questionable. Nonetheless, it is crucial that clinical trial registration is enforced in every country, by means of national legislation and/or by ethical review boards, to ensure that a complete picture of the global distribution of clinical trial research can be obtained.

Before full use can be made of the ICTRP for exploring the health R&D ‘landscape’, several other limitations need to be addressed. First, even in those countries that have legislation on the registration of clinical trials, enforced registration is often limited to trials of drugs and – sometimes – devices, phase II–IV trials, and trials that recruit subjects in the country where the legislation is implemented. This problem has been recognized in the United States of America, where new legislation to ensure that all clinical trials of interventions are registered has been proposed. There also remain concerns about the quality of the data entered into the registered records of clinical trials and about problems with the unique identification of trials, which can lead to duplicate registration.

Finally, the extraction, aggregation and analysis of the data in the ICTRP database currently require substantial manual labour. The formats of some of the data items differ across the registries covered by the ICTRP, which makes the automated aggregate analysis of data impossible. To remedy this limitation, the staff of the ICTRP are working with individual registries to harmonize the data recording formats across all of the registries that are covered by the platform. An alternative solution would be the development of algorithms to translate the variable information from individual registries into a common format and then classify the information into meaningful categories. ClinicalTrials.gov, one of the registries that provide data to the ICTRP, has already shown that the development of such data classification algorithms is feasible. Developing similar aggregation algorithms for the ICTRP – and making both the aggregated data and the results of the analysis of those data publicly available – would be an important step forward not only for the ICTRP but also for clinical trial transparency on a global scale.

In conclusion, this study shows that WHO’s ICTRP constitutes a valuable resource for assessing the global distribution of clinical trials and for informing policy development and priority setting for health R&D. The findings of this study demonstrate that there is little correlation between burden of disease and the global distribution of clinical trial research and that populations in lower-income countries receive much less attention, in terms of clinical trial research, than populations in high-income countries. A more detailed understanding of the global health R&D ‘landscape’ is needed to inform future R&D priorities. The ICTRP is one of several resources of information that will need to be ‘triangulated’ to acquire a complete picture of what health R&D is being conducted, where and how it is being conducted, and who is conducting it. The ICTRP would constitute an essential part of any global observatory on health R&D. To increase the usefulness of the ICTRP further, it is important that the enforcement of clinical trial registration be increased, that the quality of the data in registered records be improved and that more possibilities for automated aggregate data analysis on the ICTRP be created.
Use of data from registered clinical trials to identify gaps in health R&D

ACKNOWLEDGEMENTS

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Use of data from registered clinical trials to identify gaps in health R&D

George Institute for International Health; 2008.


Finding better ways to fill gaps in pediatric health research

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Viergever RF, Rademaker CMA.
Finding better ways to fill gaps in pediatric health research.
Pediatric health research and development (R&D) has long lagged behind health R&D for adults. Methodological and ethical challenges associated with pediatric research increase the costs of running pediatric trials, while the market for pediatric products is relatively small. The subsequent knowledge gaps and lack of child-specific product development have resulted in high off-label and unlicensed medication prescription rates in children. The past decade has seen increased recognition of this problem and both the US and the EU have implemented legislative measures to stimulate pediatric health R&D by providing incentives and funding for pediatric studies and by requiring pediatric studies for new drug applications when appropriate. While these measures have led to an increase in the number of pediatric trials being conducted and to several knowledge gaps being addressed, the trials remain largely driven by market incentives and evaluations of the measures in the US and the EU show that other areas remain neglected. Moreover, the majority of the global pediatric disease burden lies with populations in low- and middle-income countries (LMICs), for whom the lack of health R&D remains a significant problem.

To better understand what gaps exist in the current pediatric health R&D landscape – with respect to medicines development but also to other pediatric R&D areas such as the development of non-medicinal interventions or health systems research – it is necessary to have information on what R&D is needed and on what R&D is already being undertaken. Unfortunately, such information is not always available. Particularly, our knowledge of what health R&D is being conducted globally, where it is being conducted, by whom and how, is limited.

Mapping the health R&D landscape requires a triangulation of different resources of information on R&D inputs (e.g. investments), R&D processes (e.g. clinical trials) and R&D outputs (e.g. publications or products). Recently, we conducted an evaluation of registered clinical trials on the World Health Organization’s (WHO) International Clinical Trials Registry Platform (ICTRP). Previous analyses have shown a discrepancy between pediatric burden of disease and the amount of clinical trial research devoted to pediatric populations. Our analysis confirms this finding for LMICs, but not for high-income countries (HICs) (Table 8.1). However, in comparing the volume of clinical trial research in adults to that in children, more has to be taken into account than burden of disease. The total pediatric burden of disease in HICs is seven times lower than the adult burden. Yet, 70% of all recent medicines applications in Europe required pediatric investigation plans (PIPs). Taking this more nuanced observation as a measure for how many pediatric trials are needed, our data support the conclusion that there are fewer clinical trials for children, as compared with adults, both in LMICs and in HICs.

Our analysis also provides insight into gaps within the pediatric R&D landscape. Both in HICs and in LMICs, fewer clinical trials are registered for younger age groups, both in absolute numbers and as compared to the burden of disease (Table 8.1). Since the percentage of
Finding better ways to fill gaps in pediatric health research

children using a prescription drug is relatively high in the first year of life and off-label and unlicensed prescribing rates are particularly high for neonates, this finding supports the conclusion that the age distribution of children participating in trials does not reflect the need for R&D. In addition, we found fewer registered trials for communicable, maternal, perinatal and nutritional conditions (22% of trials; 71% of the global burden) than for non-communicable diseases (74% of trials; 21% of the global burden). This disparity is also present in adult trials, but is larger for pediatric trials, potentially reflecting that the lack of health R&D for populations in developing countries disproportionally affects children.

Knowledge of imbalances in the global distribution of pediatric clinical trial research is essential to be able to address gaps in the pediatric health R&D landscape. However, clinical trials constitute only one part of health R&D. More information is needed to obtain a complete picture of what pediatric health R&D is being conducted. For instance, another important approach is to analyse funding flows towards health R&D. This is not an easy task – many funders do not publicly report their health R&D spending (such data are available, for example, for only 37% of all countries). The funders that do report spending data use different classification schemes to categorize their spending (into health topics and types of research), making aggregate analysis of what funders fund exceedingly problematic. Analysing funding flows towards health R&D for children is even more challenging, since spending data are generally not disaggregated to pediatric or adult R&D. Nonetheless, analyses from other health areas make clear that such challenges can be overcome. G-FINDER has been conducting analyses of global funding flows towards neglected disease R&D for years, building a much better knowledge base of what the largest gaps are in that area.

Besides needing information from a greater variety of sources, there is a need for more accurate information. In our own study, the numbers of trials recruiting in LMICs and the overall predilection towards non-communicable disease research need to be interpreted with caution. Although clinical trials registration is now broadly considered an ethical and scientific responsibility, compliance with trial registration remains incomplete, particularly in LMICs. This is a broader problem – all resources of information that are currently available to monitor health R&D have substantial limitations, especially with regard to data from LMICs.

In addition to more accurate information, there is a need for more detailed information, to allow for identifying specific causes of pediatric burden of disease that have remained neglected in terms of R&D. Furthermore, there is a need to go beyond looking at diseases and identify which interventions are being studied – or neglected – for each disease. In our study of the ICTRP, 63% of all pediatric trials, across all health problems, investigated drugs, biologicals or vaccines, whereas only 5% studied diagnostics (other large categories of interventions were surgery and other procedures, at 15%, and behavioral interventions, at 11%). R&D is often more focused on developing drugs and vaccines than on developing diagnostics or platform technologies.

Although the need for increased monitoring of pediatric health R&D can be partly addressed through research studies such as ours, the comprehensive nature of the information that is needed requires a more systematic approach. Additionally, there is a need for periodic monitoring, as opposed to singular studies, allowing for a continuous process of identifying the largest gaps, evaluating if they have been addressed, providing renewed attention for those that haven’t been, and identifying newly emerging gaps. To start thinking about how this can be achieved, lessons might be learned from recent suggestions aimed at stimulating health R&D for populations in developing countries, including the establishment of a global health R&D observatory to provide a comprehensive and sustainable mechanism for regular, global monitoring of health R&D.

Realizing a pediatric health R&D landscape that is more commensurate with need will be a significant challenge. Creating more clarity on precisely what the largest gaps are in the current landscape should be the first step towards this goal. To achieve this, there is a need for more accurate and more detailed information, from a greater variety of sources, monitored on a regular basis, on the current distribution of pediatric health R&D.
Tables 8.1. The age of participants in actively recruiting, interventional trials registered on the WHO International Clinical Trials Registry Platform (ICTRP) in August 2012

<table>
<thead>
<tr>
<th>AGE OF PARTICIPANTS</th>
<th>NUMBER OF TRIALS IN SAMPLE THAT RECRUITED IN AGE GROUP</th>
<th>BURDEN OF DISEASE (IN MILLION DALYS)</th>
<th>ESTIMATED NUMBER OF TRIALS ON THE ICTR PER MILLION DALYS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-income region</td>
<td>Other regions</td>
<td>Total</td>
</tr>
<tr>
<td>0-17 years</td>
<td>297</td>
<td>101</td>
<td>372</td>
</tr>
<tr>
<td>0-27 days</td>
<td>59</td>
<td>17</td>
<td>72</td>
</tr>
<tr>
<td>28-364 days</td>
<td>71</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>1-4 years</td>
<td>113</td>
<td>43</td>
<td>154</td>
</tr>
<tr>
<td>5-9 years</td>
<td>148</td>
<td>50</td>
<td>198</td>
</tr>
<tr>
<td>10-14 years</td>
<td>187</td>
<td>63</td>
<td>250</td>
</tr>
<tr>
<td>15-17 years</td>
<td>219</td>
<td>72</td>
<td>291</td>
</tr>
<tr>
<td>18-64 years</td>
<td>1794</td>
<td>357</td>
<td>2151</td>
</tr>
<tr>
<td>65+ years</td>
<td>1434</td>
<td>242</td>
<td>1676</td>
</tr>
</tbody>
</table>

Notes: Numbers are based on a 5% sample of all interventional and actively recruiting trials on the WHO ICTRP taken on 10 August 2012. The total number of trials in the sample was 2481. For 2234 trials age information was available. Numbers are disaggregated to trials recruiting in the high-income region vs. one of six other regions, as defined by the Global Burden of Disease study 2010. Estimated numbers of trials on the WHO ICTRP were calculated by multiplying numbers from the sample by 20. 95% Confidence Intervals (CIs) reflect the confidence with which the numbers, measured in our sample of records, predict true numbers for all trials on the WHO ICTRP. When summed, the numbers exceed 100% because trials regularly recruited participants from multiple age groups and multiple regions. Burden of disease for the age group 15-17 years was calculated as by Bourgeois et al. DALY = Disability-Adjusted Life Years.

It matters how one defines a ‘pediatric trial’. We defined pediatric trials as all trials which recruited in age groups <18 years of age. When pediatric trials are defined as by Bourgeois et al as ‘trials with maximum age criteria of 17 y as well as trials with a maximum age criteria of >18 y but where the midpoint of the age range is <18 y’, the total number of pediatric trials in our sample almost halved to 213. Of the 191 trials in our sample that recruited both in adults and in children, 159 (83%) were adult trials according to this categorization and only 32 (17%) pediatric trials.

Numbers for newborns are likely inflated. Our study investigated in which age groups clinical trials on the WHO ICTRP recruited according to the trials’ age inclusion criteria, but for several studies where newborns fell within the inclusion criteria, inclusion of newborns was likely only marginal given the health problem under study.
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Pharmacokinetic research in children: an analysis of registered records of clinical trials

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Pharmacokinetic research in children: an analysis of registered records of clinical trials
Pharmacokinetic research in children

ABSTRACT

Background
Reported off-label/unlicensed prescribing rates in children range from 11% to 80%. Research into pharmacokinetic profiles of children’s medicines is essential in the creation of more knowledge on the safety and efficacy of medicines in children. This study investigated how often pharmacokinetic data are collected in clinical trials of medicines in children by analysing registered records of clinical trials.

Methods
The registered records of all clinical trials in children that were recruiting on 22 May 2009 were identified on the International Clinical Trials Registry Platform (ICTRP) using a Clinical Trials in Children search filter. The records of trials in children below 12 years of age, in which the intervention was one or more medicines, were assessed for evidence that pharmacokinetic data would be collected.

Results
Of 1081 eligible trial records, 257 (24%) declared that pharmacokinetic data would be collected. Of these trials, 199 (77%) recruited in Northern America; recruitment in all other regions was below 20%. Trials recruited most often in children over 2 years of age (74%), and least often in newborn infants (32%). Most trials researched medicines in the field of cancer (29%). Trials investigated one third of the medicines that were indicated as a priority for pharmacokinetic research by the European Medicines Agency.

Conclusions
There is a need for increased knowledge of the pharmacokinetic profiles of children’s medicines. The amount of currently ongoing pharmacokinetic research does not seem to adequately address the lack of knowledge in this area. This study sets a baseline for monitoring of future progress on the amount of ongoing pharmacokinetic research in children.

INTRODUCTION

Knowledge on the efficacy and safety of medicines for children is still very limited. Off-label (outside the product license) and unlicensed (without a license for children) prescription rates in children range from 11% to 80%. Only 20-30% of drugs that have been approved by the U.S. Food and Drug Administration (FDA) in the past, were also labelled for use in children. Adult dosing cannot be logically extrapolated to paediatric dosing according to weight or age because of different pharmacokinetic and pharmacodynamic profiles in children as compared to adults. Differences in drug metabolism between children and adults also lead to differences in susceptibility to adverse drug reactions. Worryingly, adverse drug reactions have been shown to occur more frequently with off-label prescribed drugs. The magnitude of this problem is exemplified by one source which estimates that almost one quarter of all children in the US used at least one prescription drug in the last month and that the total number of drugs used per 100 children in the US over 2004 and 2005 was 338.4. To accelerate progress towards improved availability and access to safe child-specific medicines for all children below 12 years of age, the ‘Make medicines child size’ campaign was launched by the World Health Organization (WHO) in 2007.

It has been a requirement of the International Committee of Medical Journal Editors (ICMJE) since 2004 that all clinical trials be prospectively registered in a publicly available clinical trials registry in order to be considered for publication of trial results. As of April 2011 the WHO International Clinical Trials Registry Platform (ICTRP) offers a single point of access (the ICTRP Search Portal) to data from over 130,000 clinical trials made available by clinical trial registries around the world. The importance of high-quality information on clinical trials recruiting children is increasingly being recognised. The Pan African Clinical Trials Registry (PACTR) (a WHO Primary Registry to the ICTRP) has, for example, recently created a child strategy; and the European Union has implemented legislation mandating that the EudraCT database of clinical trials ‘should include a European register of clinical trials of medicinal products for paediatric use’. To improve access to information on clinical trials in children for health care workers, researchers, and patients and their parents, the ICTRP has developed a filter (referred to as the Clinical Trials in Children or CTC filter) on the ICTRP Search Portal which makes it possible to search the portal for clinical trials in children with reasonable accuracy.

Collecting pharmacokinetic data in paediatric drug trials is fundamental in the development of a larger body of evidence on the safety and efficacy of children’s medicines. The aim of this study was to assess how many registered records of clinical trials of medicines that were recruiting children and were identifiable on the ICTRP Search Portal contained evidence that pharmacokinetic data would be collected.
**METHODS**

**Data sources**

The ICTRP Search Portal imports the WHO Trial Registration Data Set (the minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered) from registries that meet WHO criteria, including ClinicalTrials.gov. As the format of each data item differs across registries, data are currently imported into the portal as text. The ICTRP publishes a hyperlink to the record in the source registry (i.e. the registry that provided the data) so users can view additional information, if required. At the time of this study, nine registries provided data to the ICTRP: The Australian New Zealand Clinical Trials Registry (ANZCTR), the Chinese Clinical Trial Register (ChiCTR), the Clinical Trials Registry - India (CTR), ClinicalTrials.gov, the German Clinical Trials Register (DRKS), the Iranian Registry of Clinical Trials (IRCT), the International Standard Randomized Controlled Trial Number Register (ISRCTN), the Netherlands National Trial Register (NTR), and the Sri Lanka Clinical Trials Registry (SLCTR).

During this study, the CTC filter operated through a search paradigm of over 4000 keywords that were compiled by consulting child health experts who identified key terms relevant to children and adolescents.

**Study selection**

The ICTRP database was searched for all recruiting, interventional clinical trials in children using the CTC filter. The resulting records were scanned manually for eligibility. To be eligible, trial records needed to describe trials that included children below 12 years of age. For trials where inclusion of participants below 12 years was unclear from the record, the record was considered eligible only when an explicit statement was present that the trial was recruiting children, or when the investigated disease was listed as child-specific in the CTC search filter keyword database. When a trial researched an intervention in pregnant mothers, records were only included when outcomes were defined for the child.

Eligible trials also needed to have at least one arm that involved the evaluation of one or more medicines. Interventions were coded to be medicines or not by using the coding system for intervention types on ClinicalTrials.gov. Interventions that were drugs, biologicals or dietary supplements were considered to be medicines. Excluded were records of trials that researched general dietary interventions (as opposed to dietary supplements), vaccines, IV fluids (without mentioning of specific substance names), oxygen and nitric or nitrous oxide treatments, transplantations or transfusions, sucrose and glucose water for treatment of pain in newborns, alcohol cleansing of intravenous materials, somatic cell transplants and transfusions, pro- and prebiotics, and surfactant treatments.

**Data extraction**

The following information was collected manually for all eligible registered records: the age of included participants, country / countries of recruitment, study phase, and nature of sponsorship. Geographical regions of the United Nations Statistics Division were used to group countries.

Age of participants was categorised according to the International Conference on Harmonisation topic E11 age classification of paediatric patients.

Eligible registered records were searched for the presence or absence of collection of pharmacokinetic data. Pharmacokinetic data were defined as parameters that describe the fate of externally administered substances to humans after administration. Both parameters of the drug and its metabolites were denoted to be pharmacokinetic data (e.g. 25(OH)D or 1,25(OH)2D levels were recorded as pharmacokinetic outcomes of vitamin D treatment). Collection of pharmacokinetic data could be mentioned in the outcome entry fields or elsewhere in the record.

It was determined whether pharmacokinetics were recorded as a primary or a secondary outcome measure (if collection of pharmacokinetic data was mentioned outside the outcome fields, it was denoted a secondary outcome measure). Furthermore, it was documented which of the following pharmacokinetic data were studied: absorption, area under the curve (AUC) of plasma or tissue concentration, autoinduction response, balance, bioavailability, breakdown, clearance, distribution, elimination, excretion, faecal clearance, faecal excretion, lowest concentration, metabolism, peak concentration, plasma half-life (t1/2), plasma or tissue concentration, renal clearance, time to lowest concentration, time to peak concentration, urinary excretion, volume of distribution, or general mentioning of pharmacokinetic data collection or a pharmacokinetic study design. Use of a population pharmacokinetic design and additional general mentioning of pharmacodynamic data collection or the use of a pharmacodynamic study design were denoted.

The primary health condition or problem studied and the drug, biological or dietary supplement that was under investigation were denoted for trials that reported collection of pharmacokinetic data. The primary health condition or problem studied was categorised according to WHO ICD-10 chapters. For drugs, biologicals and dietary supplements, we adhered to the names for the interventions as denoted in the registered record, except when proprietary names were used, which we converted to nonproprietary names. When there were multiple medicines described, but there was one main intervention, and the record lacked specification for which medicines pharmacokinetics would be determined, it was assumed that pharmacokinetics would be determined for the main intervention. The drugs, biologicals and dietary supplements that were found were compared with the medicines for which there was a priority need for pharmacokinetic data, according to the
European Medicines Agency (EMA) revised priority list for studies into off-patent paediatric medicinal products from 2008, which was the most recent version at the time of this study.20 Furthermore, we analysed the EMA 2009 and 2010 priority lists to see whether medicines from the 2008 list endured to be priorities for pharmacokinetic investigation. Lastly, to investigate whether there were trials that studied EMA priority medicines without collecting pharmacokinetic data, we searched the scientific and public titles of all studies in our sample for mentioning of the EMA priority medicines.

All records were scanned for eligibility by RFV who then, in case of inclusion, extracted and coded the data. During eligibility assessment and data extraction trial records for which data were ambiguous were further assessed by DG. Conflicts were resolved by mutual agreement. Microsoft SPSS version 16.0.1 was used for descriptive analyses of the data.

RESULTS

The ICTRP Search Portal was searched using the CTC filter on 22 May 2009 resulting in the identification of 3051 records of interventional clinical trials in children, of which 1081 were investigating one or more medicines (i.e. the intervention was a drug, biological or dietary supplement) and mentioned inclusion of children below 12 years of age. 257 (24%) of these records reported that pharmacokinetic data would be collected. The medicines that were investigated by the corresponding trials were drugs or biologicals in 209 records (81%) and dietary supplements in 48 records (19%).

The 1081 records of children’s trials reported recruitment of participants in 92 countries; the records that reported collection of pharmacokinetic data recruited in 48 countries. Of the 257 records that reported collection of pharmacokinetic data, 199 records (77%) reported recruitment in Northern America; recruitment in all other regions was below 20% (Table 9.1). Among the 824 records of trials without pharmacokinetic data collection, Northern America was also the most frequent geographical region of recruitment, but less so (57%).

Looking more closely at the age of participants being recruited in trials that reported collection of pharmacokinetic data, 81 records (32%) involved preterm or term newborn infants (0 to 27 days), 126 records (49%) infants and toddlers (28 days to 23 months), and 190 records (74%) children between the ages of 2 and 11 years.

Table 9.1.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Records from trials that reported collection of PK data (N=257)</th>
<th>Records from trials that did not report collection of PK data (N=824)</th>
<th>Total</th>
<th>Percentage of total reporting collection of PK data per age group, region, phase, or sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn infants (0 to 27 days)</td>
<td>81 32%</td>
<td>226 27%</td>
<td>307 26%</td>
<td></td>
</tr>
<tr>
<td>Infants and toddlers (28 days to 23 months)</td>
<td>126 49%</td>
<td>371 45%</td>
<td>497 25%</td>
<td></td>
</tr>
<tr>
<td>Children between the ages of 2 and 11 years</td>
<td>190 74%</td>
<td>680 83%</td>
<td>870 22%</td>
<td></td>
</tr>
<tr>
<td>Not indicated</td>
<td>3 1%</td>
<td>19 2%</td>
<td>22 -</td>
<td></td>
</tr>
<tr>
<td>Geographical region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>16 6%</td>
<td>44 5%</td>
<td>60 27%</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>26 10%</td>
<td>94 11%</td>
<td>120 22%</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>50 19%</td>
<td>217 26%</td>
<td>267 19%</td>
<td></td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>25 10%</td>
<td>61 7%</td>
<td>86 29%</td>
<td></td>
</tr>
<tr>
<td>Northern America</td>
<td>199 77%</td>
<td>469 57%</td>
<td>668 30%</td>
<td></td>
</tr>
<tr>
<td>Oceania</td>
<td>13 5%</td>
<td>83 10%</td>
<td>96 14%</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>12 5%</td>
<td>35 4%</td>
<td>47 -</td>
<td></td>
</tr>
</tbody>
</table>

Almost half of the trials that were reported to collect pharmacokinetic data were sponsored by a university or a hospital. Though there were fewer federal (15%) and industry (26%) sponsored trials performing research into medicines in children under 12 years, these trials were more likely to collect pharmacokinetic data (32% and 37% respectively) than university or hospital sponsored studies (19%).

Mention of pharmacokinetic data collection was most frequent in records of trials that were Phase 1 (62%) or Phase 1 and 2 (57%). 39% of all trials that reported pharmacokinetic data collection were Phase 1 or Phase 1 and 2, 43% were Phase 2 to 4 (in 19% of records study phase was not provided).
Pharmacokinetic research in children

Of the 257 records that reported collection of pharmacokinetic data, 56 records (22%) mentioned only the measuring of serum or tissue concentrations, and did not mention a pharmacokinetic study design, or any of the other pharmacokinetic parameters (34 of these 56 records (61%) were of trials that investigated dietary supplements). Which pharmacokinetic data were reported to be collected in records is shown in more detail in Figure 9.1. 124 records (48%) reported pharmacokinetic data as a primary outcome and 163 (63%) reported pharmacokinetic data as a secondary outcome (overlap is due to mentioning of pharmacokinetic data as both a primary and a secondary outcome measure in 30 records).

11 records (4%) mentioned use of a population pharmacokinetic design. 52 records (20%) mentioned pharmacodynamic data collection or the use of a pharmacodynamic study design in addition to pharmacokinetic data collection (out of the 824 records that did not report pharmacokinetic data collection, 12 records mentioned collection of pharmacodynamic data).

The primary health condition or problem studied in trials that collected pharmacokinetic data was most often cancer (29%) (Figure 9.2). The distribution of health conditions or problems studied differed per age group, with less of a propensity for cancer research among the group of newborn infants (Figure 9.3). A detailed oversight of the medicines that were investigated by trials that reported collection of pharmacokinetic data can be found in Web Only File 1.

Of the 28 medicines on the EMA revised priority list for studies into off-patent paediatric medicinal products from 2008 for which collection of pharmacokinetic data was indicated to be a priority, we found 9 medicines (32%) to be investigated in trials identified in our search (Table 9.2). Of the 28 medicines that were EMA priorities in 2008, 14 (50%) were still a priority in 2009 and 12 still in 2010 (43%). Of the 9 medicines for which we found pharmacokinetic data collection, 2 were still a priority in 2010 (22%). Of the 19 medicines for which we did not find pharmacokinetic data collection, 10 were still a priority in 2010 (53%).

### Figure 9.1.
**Collected pharmacokinetic (PK) data in paediatric drug trials**

Notes: Every first bar represents which pharmacokinetic data were reported as a primary outcome, every second bar those that were reported as a secondary outcome.
Figure 9.2.
Investigated health conditions or problems in trials that collected pharmacokinetic data

Figure 9.3.
Investigated health conditions or problems per age group

Notes: The graph on the top left displays the distribution of health conditions or problems studied in trials that recruited only newborn infants; the top right graph displays this information for trials that recruited only infants/toddlers; the middle left graph for trials that recruited only children > 2 years of age; the middle right graph for trials that recruited newborn infants and infants/toddlers; the lower left graph for trials that recruited infants/toddlers; the lower right graph for trials that recruited newborn infants, infants/toddlers, and children > 2 years of age.

Notes: ICD-10 = Tenth Revision of the International Classification of Diseases

Number of records

ICD-10 Disease categories

Healthy

IX and X: External causes of morbidity and mortality and the consequences thereof

XVII: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

XII: Congenital malformations, deformations and chromosomal abnormalities

XIII: Symptomatic and sequelae of perinatal period

XIV: Prenancy, childbirth and the puerperium

X: Diseases of the respiratory system

IX: Diseases of the circulatory system

VIII: Diseases of the ear and mastoid process

VII: Diseases of the eye and adnexa

VI: Diseases of the nervous system

V: Mental and behavioural disorders

IV: Endocrine, nutritional and metabolic diseases

III: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

II: Neoplasms

I: Certain infectious and parasitic diseases

ICD-10 Disease categories

Newborn infants only

Infants / toddlers only

Children > 2 years of age only

Newborn infants and infants / toddlers

Infants / toddlers and children > 2 years of age

Newborn infants, infants / toddlers, and children > 2 years of age
Pharmacokinetic research in children

and children > 2 years of age, and the lower right graph for trials that recruited newborn infants, infants/toddlers, and children > 2 years of age.

Academic and public titles of the 1081 records in the sample were searched for the names of the 19 medicines that we did not find pharmacokinetic data collection for in any record. Eight (42%) of these medicines were identified in 29 trial records as an intervention.

DISCUSSION

To our knowledge, this is the first study to report on the global activity of collection of pharmacokinetic data in clinical trials in children. It assessed all paediatric trials that were recruiting on 22 May 2009, as registered at clinical trial registries that are a part of the ICTRP registry network. Of 1081 records of trials researching medicines in children, one quarter reported that they would be collecting pharmacokinetic data. So is this a lot, or a little? In view of the current paucity of knowledge on safety and efficacy of children’s medicines, the degree to which this knowledge is in arrears as compared to our understanding of adult medication, and the widespread prescribing of medicines to children, we would argue that it is not enough.

The fact that only one fifth of the records that mentioned collection of pharmacokinetic data also mentioned to be studying pharmacodynamics adds to this conclusion. Additionally, our analysis of the types of trials researching pharmacokinetics show that there might be significant pharmacokinetic research gaps in terms of geographical area, studied diseases and age categories. Over 75% of all studies recruited participants in Northern America, while recruitment in all other geographical regions was below 20%. This unequal distribution appears to exist for all paediatric drug trials, but especially for studies collecting pharmacokinetic data. Given the existence of interethnic differences in pharmacological effects on the body and that many diseases are not prevalent in Northern America, this gap is a reason for concern. Similarly, the distribution of pharmacokinetic research across different ICD-10 disease categories suggests that the lacking knowledge of pharmacokinetics in children is only marginally addressed in some areas. Previous studies have shown that paediatric research in general often does not address priority research areas. Finally, although knowledge on pharmacokinetic profiles in children is at an inadequate level for all age groups, the least is known about pharmacokinetics in the youngest age group of neonates. This study shows that this age group, worryingly so, is also the least likely to be studied.

Table 9.2.
European Medicines Agency (EMA) 2008 priorities for pharmacokinetic (PK) analysis

<table>
<thead>
<tr>
<th>Name of medicine</th>
<th>Notes</th>
<th>Investigated in trial records identified on the ICTRP?</th>
<th>Still in 2009 EMA priorities?</th>
<th>Still in 2010 EMA priorities?</th>
<th>Medicine investigated in trials without collection of PK data?</th>
<th>In how many trial records?</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mercaptopurine</td>
<td>in infants</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actinomycin</td>
<td>below the age of 6 years</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asparaginase</td>
<td>in infants</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td></td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td></td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>below the age of 3 years</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>10</td>
</tr>
<tr>
<td>Cladribine</td>
<td></td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Clopidine</td>
<td></td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>6</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>data on PK of metabolites</td>
<td>yes, including metabolites</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>in infants</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>in infants</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td></td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Foscarnet</td>
<td></td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>above 6 years and adolescent</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td></td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>parenteral formulation</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Levamisole</td>
<td></td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Menopenem</td>
<td>below 3 months of age</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>See</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>4</td>
</tr>
<tr>
<td>Milrinone</td>
<td></td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>2</td>
</tr>
</tbody>
</table>
The paediatric research community has much to gain from the inclusive database of clinical trials in children that the ICTRP search portal provides through its Clinical Trials in Children search filter. Clinical trials registration allows for doctors and patients and their parents to inform themselves more adequately about trials open to recruitment. It is likely to promote collaboration among researchers, by facilitating knowledge transfer on currently ongoing research, thus also preventing duplication of research. Furthermore, it has the potential to contribute to establishing more reliable research evidence by aiding in the prevention of selective reporting and publication bias. Although the ethical and legal pressure to adequately report the results of clinical trials is increasing, selective reporting and publication bias are still important problems. If all trials (and their outcomes) are registered before start of the trial, researchers that withhold publication of trial results or the original outcomes because of negative results can be held accountable. Finally, clinical trials registration facilitates priority setting in paediatric research, identifying gaps between burden of disease and research efforts in different therapeutic areas. This study confirms that analysis of clinical trials identified on the ICTRP database can be a powerful tool to comprehensively assess the amount of currently ongoing research in a particular research area.

The need for improved availability of and access to safe child-size medicines has received growing attention in recent years. WHO addresses this issue through its ‘make medicines child size’ campaign. Other initiatives that promote trials on medicines in children include US and EU legislation. While these legislative measures are a positive development and have resulted in an increased number of trials being conducted in the paediatric population, they have not been free from critique. Given how crucial pharmacokinetic research is in the creation of more knowledge on the safety and efficacy of medicines in children and the concerns that the present study raises on the amount of such research currently being conducted, it is of great importance that the collection of pharmacokinetic data in clinical trials in children continues to be monitored in the future. The Clinical Trials in Children search filter of the ICTRP offers a platform to do so.

**WEB ONLY FILES**

File name: Web Only file 1.

Title of data: Medicines that were researched in trials that collected pharmacokinetic data

Description of data: This file describes the names of the medicines (drugs, biologicals or dietary supplements) as mentioned in the 257 trial records that reported collection of pharmacokinetic data.

This Web Only file has not been admitted to this thesis but can be accessed at: [http://bmjopen.bmj.com/content/1/1/e000221.full](http://bmjopen.bmj.com/content/1/1/e000221.full)

**ACKNOWLEDGEMENTS**

The authors are indebted to Ghassan Karam for his help in attaining a random sample of registered records from the ICTRP database, to Dr Anna Ridge for her help in designing the study, and to Dr Suzanne Hill for her help in designing the study and reviewing early drafts of this manuscript.
Pharmacokinetic research in children

**BOX 9.1.**

**CHAPTER SUMMARY**

**Article focus**
- The main aim of this study was to assess how many registered records of clinical trials of medicines that were recruiting children and were identifiable on the ICTRP Search Portal contained evidence that pharmacokinetic data would be collected.
- Secondary aims were to assess which pharmacokinetic data were collected and what types of trials were reporting pharmacokinetic data.

**Key messages**
- This study quantifies, for the first time, the amount of currently ongoing research into pharmacokinetic profiles of medicines in children.
- It shows how much and what kind of pharmacokinetic research is being carried out worldwide as registered at clinical trial registries and analyses the types of trials that perform this research.
- It sets a baseline for future studies, to monitor progress in the amount of pharmacokinetic research that is performed in children.

**Strengths and limitations of this study**
- Our study is one of the first studies of its kind, in that it has created a comprehensive oversight of the amount of ongoing research in one particular research area, by analysing information in registered records of clinical trials. Using information in clinical trial databases as such offers a unique, and currently underused, method for informing future research prioritisation efforts at a policy level (in our case of paediatric off-patent medicines by the European Medicines Agency).
- This study is limited by the quality of information in the included registered records. Studying registered records of clinical trials is not the same as studying how clinical trials were in fact conducted. However, in the absence of open access to complete trial protocols we have no other choice than to use the information entered into a trial registry for this type of analysis.

**REFERENCES**
22. Pandolfini C, Bonati M. Something is moving in European drug research for children, but a more focused effort concerning all therapeutic needs is necessary. Arch Dis Child. 2006;91:715.
OBJECTIVE 3
To evaluate what barriers there are to the meaningful utilization of registered clinical trial data and how these may be mitigated

“Good priority setting starts with good information.”
10

The quality of registration of clinical trials

Based on


The quality of registration of clinical trials

ABSTRACT

Background
Lack of transparency in clinical trial conduct, publication bias and selective reporting bias are still important problems in medical research. Through clinical trials registration, it should be possible to take steps towards resolving some of these problems. However, previous evaluations of registered records of clinical trials have shown that registered information is often incomplete and non-meaningful. If these studies are accurate, this negates the possible benefits of registration of clinical trials.

Methods & Findings
A 5% sample of records of clinical trials that were registered between 17 June 2008 and 17 June 2009 was taken from the International Clinical Trials Registry Platform (ICTRP) database and assessed for the presence of contact information, the presence of intervention specifics in drug trials and the quality of primary and secondary outcome reporting. 731 records were included. More than half of the records were registered after recruitment of the first participant. The name of a contact person was available in 94.4% of records from non-industry funded trials and 53.7% of records from industry funded trials. Either an email address or a phone number was present in 76.5% of non-industry funded trial records and in 56.5% of industry funded trial records. Although a drug name or company serial number was almost always provided, other drug intervention specifics were often omitted from registration. Of 3643 reported outcomes, 34.9% were specific measures with a meaningful time frame.

Conclusions
Clinical trials registration has the potential to contribute substantially to improving clinical trial transparency and reducing publication bias and selective reporting. These potential benefits are currently undermined by deficiencies in the provision of information in key areas of registered records.

INTRODUCTION

Many instances of unethical research conduct by clinical trial sponsors and investigators have come to light over the past decade. The types of misconduct vary and include not obtaining approval from research ethics committees, not obtaining informed consent from trial participants and the fabrication of data.1–5 Despite the ethical obligation to accurately report the results of research in humans,6 some trial sponsors have deliberately withheld negative outcome information when publishing the findings of clinical trials, and when making the trial findings available to regulatory authorities.7–9 Such behaviour is particularly concerning when the misconduct involves trials recruiting participants in low and middle income countries with deficient oversight mechanisms.5

Prospectively registering clinical trials can potentially prevent at least some of this misconduct from occurring, specifically selective reporting, by putting key protocol information about each trial in the public domain, ideally before the first participant is recruited to the study. Five years have now passed since the International Committee of Medical Journal Editors (ICMJE) first published its statement requiring registration as a precondition of publication,10 and the World Health Assembly approved the establishment of the International Clinical Trials Registry Platform (ICTRP) by the World Health Organization (WHO). Today the ICTRP provides free access via a single web portal to more than 120,000 records of registered trials made available by clinical trial registries around the world.11 In the intervening years the number of countries and agencies that have created and implemented their own policies on trial registration has increased, including the World Medical Association which now explicitly states in the Declaration of Helsinki that prospective registration is an ethical requirement.6,12–24

Prospective registration can only contribute to the more ethical conduct of clinical trials however, if all of the key information about the trial is registered, and the registered data are meaningful. The ICMJE agrees that quality is important and states that missing or uninformative entries in any of the fields required by the WHO 20-item Trial Registration Data Set is inadequate.25,26 The quality of registered data has been called into question of late, with particular concerns regarding the quality of contact information,27,31 intervention details,27,30–33 and the outcomes (and outcome measures) being used.27,31–33 Poor data quality raises doubt on the ability of trial registration to meet the challenge of achieving research transparency, including the ability to adequately address publication bias and selective reporting, and reducing the amount of wasted research.37–39

The objective of this study was therefore to determine whether registered records of clinical trials contained complete and meaningful data for key items in the WHO Trial Registration Data Set.25 Given the particular concern regarding the quality of contact information, intervention details, and outcome information, it was agreed that these data items would be the focus of the study.
METHODS

A random 5% sample of all clinical trial records of trials registered as interventional between 17 June 2008 and 17 June 2009 was taken from the ICTRP database. Records of trials that were registered as observational, records that pertained to US Food and Drug Administration (FDA) lockbox device trials and records that were duplicate records (due to registration of a trial in more than one register) were not eligible for the sample. For trials with multiple records the record with the earliest registration date was considered eligible. At the time the sample was taken the database included trials registered in nine different registries.

About the data

The ICTRP Search Portal imports the WHO Trial Registration Data Set from registries that meet WHO criteria, including ClinicalTrials.gov. As the format of each data item differs across registries, data is currently imported into the portal as text. The ICTRP publishes a hyperlink to the record in the source registry (i.e. the registry that provided the data) so users can view additional information, if required.

Data extraction

Registry name, trial ID, target sample size, recruitment status, date of first enrolment and the public and scientific title for each record were downloaded from the ICTRP database and imported into Excel on 17 June 2009.

During manual searching of records, it became clear that several records of trials that were registered as interventional were in fact records of observational trials, diagnostic accuracy trials or treatment protocols for continuation of treatment after inclusion in a study protocol. These records were excluded from further data extraction.

Descriptive information on study phase, study design, randomization status and inclusion criteria for gender and age of participants was extracted manually from the complete registered record in the source registry. Data on interventions and sponsorship was also extracted manually and was then coded. The system used to code interventions was adapted from the codes used for intervention types on ClinicalTrials.gov. Primary sponsors were coded as being foundation, government, industry, university/hospital, or other. Trials were coded as being industry funded (primary sponsor was industry), partially industry funded (primary sponsor was non-industry, but secondary sponsor or source of monetary or material support was industry) or non-industry funded.

Outcome measures

The number of primary and secondary outcomes per record was collected. Each primary and secondary outcome was evaluated for specificity, using a classification system adapted from the system used by Zarin et al in their assessment of quality of outcomes. If a record contained multiple outcomes, all were assessed separately. Outcomes were classified as being a specific measure, a domain, vague, an unexplained abbreviation, or a part of safety monitoring.

Besides assessing the specificity of each outcome, the presence or absence of a time frame was collected for every outcome. Some outcomes assessed the duration of an event, the time to an event or were safety monitoring outcomes. For these outcomes, reporting a time frame is not possible, and the timeframe was therefore denoted as irrelevant. Time frames were denoted to be not meaningful when they did not specify a point in time when the outcome was to be measured.

Only outcomes mentioned in the outcome fields were assessed. Other texts in the record were scanned for additional information on mentioned outcomes.
The quality of registration of clinical trials

Internal inconsistencies in study design
Internal inconsistencies in study design fields were identified. Internal inconsistencies were defined as records with multiple descriptors that were not compatible, such as ‘single-group’ and ‘controlled or randomized’, ‘open-label’ and ‘blinded’, and ‘double-blinded’ without subject or investigator blinding.

Pilot
Before starting data extraction a small pilot project was carried out on 25 random records from the ICTRP database to test the assessment framework. Results of the pilot were discussed by DG and RV and the framework was subsequently adapted.

Assessment rules
All records were assessed for eligibility by RV who then extracted and coded the data. During eligibility assessment and data extraction trial records that were not covered by the framework, or where that was ambiguous, were further assessed by DG. Conflicts were resolved by mutual agreement. A more detailed overview of the rules used in all assessments is provided in supporting information file S1.

Analysis
Odds ratios and Pearson’s chi-squares were calculated to assess the relationship between sources of funding and the presence of contact details. For this purpose, partially industry funded trials and non-industry funded trials were grouped together.

Completeness of registration of intervention specifics was analysed according to funding source and trial phase. A binary outcome variable was used that could be incomplete versus complete registration of the intervention. Complete registration entailed the reporting of drug name, dose, duration, frequency and route. Funding source was categorized as in the analysis of contact details. Trial phase was categorized to be Phase 0 or I versus other (some trials were registered as being Phase I & II; these were categorized as other). Regression analysis with robust estimation of variance for clustered samples was used to assess whether these variables influenced completeness of registration of intervention specifics.

Quality of registration of primary outcomes was analysed according to funding source, sample size category, trial phase and intervention category. A binary outcome variable was used that could be registration of a specific measure with a meaningful time frame present or for which a time frame was irrelevant, versus any other outcome. Funding source was categorized as in the analysis of contact details. Trial phase was categorized as in the analysis of intervention specifics. Sample size was categorized as being <100 participants versus 100 or more participants. Interventions were categorized to being either drug, biological or vaccine versus other interventions. Regression analysis with robust estimation of variance for clustered samples was used to assess whether these variables influenced the quality of registration of primary outcomes.

Statistical analyses were performed using SPSS version 15.0.1 and STATA version 11.1.

Figure 10.1.
Flowchart

ICTRP search 17 June 2009
Inclusion criteria: All records of trials that were registered as interventional between 17 June 2008 and 17 June 2009
Exclusion criteria: • US FDA lockbox device trial records • Duplicate records

15,080 records
5% sample
754 records
1 record withdrawn by registry
753 records
22 records of observational studies, diagnostic accuracy studies or treatment continuation protocols
731 records included for data extraction
Trials that investigated drugs, biologicals or vaccines
439 records included for subset analysis of quality of registration of interventions
The quality of registration of clinical trials

RESULTS

There were 754 records in our 5% sample. One record was withdrawn by the registry and could not be assessed. 22 records were excluded from data extraction because the corresponding trials were of an observational or diagnostic accuracy study design or were a treatment protocol for continuation of treatment after inclusion in a study protocol. A total of 731 records were included for data extraction, of which 439 investigated drugs, biologicals or vaccines (Figure 10.1).

All information that had to be extracted manually from the registered records was collected between 17 June 2009 and 11 August 2009. Baseline data on registry name, primary sponsor category, intervention type, study phase, study design, randomization status and inclusion criteria for gender of participants are presented in Table 10.1.

Records were additionally checked for the presence of entries in the fields for recruitment status, date of first enrolment and the public and scientific title. The former three were present in all records, the latter was reported in 700 records (95.8%). Furthermore, information was collected on sample size and age of participants. Sample size was reported in 721 records (98.6%). The median target sample size for these records was 68 [IQR 30 – 200]. Age of participants was reported in 700 records (95.8%). 89 records (12.2%) mentioned inclusion of participants <18 years of age. Finally, registration dates and dates of first enrolment were compared. The majority of records in our sample did not provide a day for the date of first enrolment but only a month and a year, which limited this analysis to comparing the month in which trials were registered to the month in which the first participant was recruited. The registration date was in a later month than the date of first enrolment in 53.4% of records (median: 10 months). This difference was more than one month in 43.6% of records. Registration date and date of first enrolment were in the same month in 20.7% of records. The registration date was in an earlier month than the date of first enrolment in 26.0% of records (median: 2 months).

Quality of registration of contact information

Overall, 81.0% of records reported a name of a contact person (n=592). 59.4% of records provided an email address (n=434) and 64.2% of records a telephone number (n=469). 68.7% of records provided either an email address or a telephone number (Table 10.2).

Industry funded trials were less likely to mention a name in their registered records than partially industry funded trials or non-industry funded trials (OR = 15.9, 95% CI: 9.9 – 25.5, p<0.001). Industry funded trials were also less likely to mention an email address in their registered records (OR = 3.6, 95% CI: 2.6 – 4.9, p<0.001) or to mention a telephone number (OR = 3.1, 95% CI: 2.2 – 4.2, p<0.001). There were no differences in the presence of contact details between partially industry funded trials and non-industry funded trials (p=0.28, p=0.18 and p=0.13 respectively).

Table 10.1. General descriptive information

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>NUMBER OF RECORDS</th>
<th>PERCENTAGE OF RECORDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registry name a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANZCTR</td>
<td>26</td>
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</tr>
<tr>
<td>ChiCTR</td>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>ClinicalTrials.gov</td>
<td>628</td>
<td>85.9</td>
</tr>
<tr>
<td>CTRI</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>DRKS</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>IRCT</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>ISRCTN</td>
<td>39</td>
<td>5.3</td>
</tr>
<tr>
<td>NTR</td>
<td>16</td>
<td>2.2</td>
</tr>
<tr>
<td>SLCTR</td>
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<td>0.1</td>
</tr>
<tr>
<td>Primary sponsor</td>
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<td></td>
</tr>
<tr>
<td>Foundation</td>
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<td>1.4</td>
</tr>
<tr>
<td>Government</td>
<td>39</td>
<td>5.3</td>
</tr>
<tr>
<td>Industry</td>
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</tr>
<tr>
<td>University / hospital</td>
<td>398</td>
<td>54.4</td>
</tr>
<tr>
<td>Other b</td>
<td>37</td>
<td>5.1</td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Intervention type c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>385</td>
<td>52.7</td>
</tr>
<tr>
<td>Biological / vaccine</td>
<td>82</td>
<td>11.2</td>
</tr>
<tr>
<td>Device</td>
<td>49</td>
<td>6.7</td>
</tr>
<tr>
<td>Procedure / surgery</td>
<td>69</td>
<td>9.4</td>
</tr>
<tr>
<td>Radiation</td>
<td>23</td>
<td>3.1</td>
</tr>
<tr>
<td>Behavioural</td>
<td>76</td>
<td>10.4</td>
</tr>
<tr>
<td>Genetic d</td>
<td>14</td>
<td>1.9</td>
</tr>
<tr>
<td>Dietary supplements</td>
<td>53</td>
<td>7.3</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>23</td>
<td>3.1</td>
</tr>
<tr>
<td>Organizational</td>
<td>21</td>
<td>2.9</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>9</td>
<td>1.2</td>
</tr>
<tr>
<td>Other</td>
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<td>2.2</td>
</tr>
<tr>
<td>Study phase e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>1.4</td>
</tr>
<tr>
<td>1</td>
<td>106</td>
<td>14.5</td>
</tr>
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</table>
The quality of registration of clinical trials

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>NUMBER OF RECORDS</th>
<th>PERCENTAGE OF RECORDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>38</td>
<td>5.2</td>
</tr>
<tr>
<td>II</td>
<td>122</td>
<td>16.7</td>
</tr>
<tr>
<td>II &amp; III</td>
<td>16</td>
<td>2.2</td>
</tr>
<tr>
<td>III</td>
<td>101</td>
<td>13.8</td>
</tr>
<tr>
<td>IV</td>
<td>85</td>
<td>11.6</td>
</tr>
<tr>
<td>Not specified</td>
<td>253</td>
<td>34.6</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Study design</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Single arm</td>
<td>162</td>
<td>22.2</td>
</tr>
<tr>
<td>Controlled</td>
<td>458</td>
<td>62.7</td>
</tr>
<tr>
<td>Crossover</td>
<td>79</td>
<td>10.8</td>
</tr>
<tr>
<td>Not specified</td>
<td>32</td>
<td>4.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomization f</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>518</td>
<td>70.9</td>
</tr>
<tr>
<td>Non-randomized</td>
<td>23</td>
<td>3.1</td>
</tr>
<tr>
<td>Not specified</td>
<td>29</td>
<td>4.0</td>
</tr>
<tr>
<td>Not applicable</td>
<td>161</td>
<td>22.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>39</td>
<td>5.3</td>
</tr>
<tr>
<td>F</td>
<td>79</td>
<td>10.8</td>
</tr>
<tr>
<td>Both</td>
<td>599</td>
<td>81.9</td>
</tr>
<tr>
<td>Not specified</td>
<td>14</td>
<td>1.9</td>
</tr>
<tr>
<td>Total per category</td>
<td>731</td>
<td>100</td>
</tr>
</tbody>
</table>

Quality of registration of interventions involving drugs, biologicals or vaccines

There were 439 records of trials that investigated drugs, biologicals or vaccines. Intervention specifics were recorded for 726 experimental or active comparator arms. A name was reported in 713 arms (98.2%). For dose, duration of the intervention, frequency of administration and route of administration, information was present in 512 (70.5%), 508 (70.0%), 550 (75.8%) and 535 (73.7%) arms respectively. 321 arms (44.2%) were complete in registering intervention specifics.

Multiple logistic regression analysis showed that funding source was not a significant predictor of completeness of registration of intervention specifics (p=0.39), but that study phase was (p<0.001). Additional univariate analyses were performed, which confirmed that funding source was not a significant predictor of intervention registration quality (p=0.34) and that trials that were Phase 0 or I were more likely to be complete in reporting intervention specifics than other trials (OR = 2.7, 95% CI: 1.5 – 4.9, p<0.001).

Quality of registration of outcome measures

The 731 included trial records reported 1271 primary outcomes and 2372 secondary outcomes. 66.2% of records reported one primary outcome, 17.5% reported two, 6.0% reported three and 9.2% reported four or more. The maximum number of primary outcomes reported in one record was 24. Eight records (1.1%) reported no primary outcome at all, and 149 records reported no secondary outcomes (20.4%). The degree of specificity of reported outcomes was assessed (Table 10.3). 38.2% of primary outcomes, 33.2% of secondary outcomes and 34.9% of primary and secondary outcomes combined were specific measures, for which a time frame was irrelevant or for which a meaningful time frame was present.

Table 10.2.
Presence of contact details by funding source

<table>
<thead>
<tr>
<th></th>
<th>NAME</th>
<th>EMAIL</th>
<th>TELEPHONE NR.</th>
<th>EMAIL OR TEL. NR.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry (N=246)</td>
<td>N</td>
<td>132</td>
<td>96</td>
<td>115</td>
</tr>
<tr>
<td>%</td>
<td>53.7</td>
<td>39.0</td>
<td>46.7</td>
<td>56.5</td>
</tr>
<tr>
<td>Partially industry (N=76)</td>
<td>N</td>
<td>74</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>%</td>
<td>97.4</td>
<td>63.2</td>
<td>65.8</td>
<td>65.8</td>
</tr>
<tr>
<td>Non-industry (N=408)</td>
<td>N</td>
<td>385</td>
<td>289</td>
<td>303</td>
</tr>
<tr>
<td>%</td>
<td>94.4</td>
<td>70.8</td>
<td>74.3</td>
<td>76.5</td>
</tr>
<tr>
<td>Overall (N=731) a</td>
<td>N</td>
<td>592</td>
<td>434</td>
<td>469</td>
</tr>
<tr>
<td>%</td>
<td>81.0</td>
<td>59.4</td>
<td>64.2</td>
<td>68.7</td>
</tr>
</tbody>
</table>

Notes:
- a For one trial, no primary sponsor was registered.

Notes:
- a Registry acronyms stand for: Australian New Zealand Clinical Trials Registry (ANZCTR), Chinese Clinical Trial Register (ChiCTR), Clinical Trials Registry - India (CTRI), German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), International Standard Randomized Controlled Trial Number Register (ISRCTN), The Netherlands National Trial Register (NTR), Sri Lanka Clinical Trials Registry (SLCTR).
- b Other sponsors consisted of persons that were registered as primary sponsor, non-governmental organizations, collaborative research institutions and clinical research organizations.
- c Overlap was possible, total in this category is greater than 731.
- d Genetic interventions consisted of gene transfer therapy and somatic cell transplants.
- e The presence of study phase in records was analysed separately for trials in drugs, biologicals or vaccines. Of 439 trials researching these types of interventions, study phase was reported in 370 records (84.3%).
- f For single arm trials, randomization is not applicable. However, one single arm trial was registered as being randomized.
Multiple logistic regression analysis showed that funding source \( (p=0.30) \), target sample size \( (p=0.93) \), intervention category \( (p=0.39) \) and study phase \( (p=0.70) \) were all not significant as predictors for the reporting of specific measures with a meaningful time frame present (or irrelevant). Additional univariate analyses were performed, which confirmed that none of the dependent variables were significant predictors of outcome registration quality \( (p=0.24, p=0.33, p=0.49 \text{ and } p=0.46 \text{ respectively}) \).

### Table 10.3.
Degree of specificity of primary and secondary outcomes

<table>
<thead>
<tr>
<th>Classification (%)</th>
<th>Primary Outcomes (N=1271)</th>
<th>Secondary Outcomes (N=2372)</th>
<th>Primary and Secondary Outcomes (N=3643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific measure</td>
<td>47.1</td>
<td>42.5</td>
<td>44.1</td>
</tr>
<tr>
<td>Domain</td>
<td>36.7</td>
<td>38.7</td>
<td>38.0</td>
</tr>
<tr>
<td>Vague</td>
<td>5.4</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Unexplained abbreviation</td>
<td>3.5</td>
<td>4.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Safety monitoring</td>
<td>7.3</td>
<td>7.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Time (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time present</td>
<td>65.9</td>
<td>62.7</td>
<td>63.8</td>
</tr>
<tr>
<td>Time present, not meaningful</td>
<td>10.8</td>
<td>13.7</td>
<td>12.7</td>
</tr>
<tr>
<td>Time absent</td>
<td>7.7</td>
<td>9.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Time irrelevant</td>
<td>15.6</td>
<td>14.4</td>
<td>14.8</td>
</tr>
</tbody>
</table>

**Internal inconsistencies in study design**

Internal inconsistencies in the study design fields were identified in 9.3% of records.

### DISCUSSION

To be able to fulfill the promise of clinical trials registration, it is of paramount importance that registration is comprehensive, complete and accurate. That is, that all trials in all countries are registered, that meaningful data are registered for every item in the WHO Trial Registration Data Set, and that registered data are correct and up-to-date. This study confirms the findings of similar studies that have shown that the quality of registered trial data is a significant problem and that it needs to be improved.

There should be clearly assigned responsibility to a named Principal Investigator in all registered records of clinical trials to facilitate investigator accountability and transparency. By Principal Investigator (PI) we mean ‘the individual who is responsible and accountable for conducting the clinical trial’. In 2008 Sekeres et al examined 1388 clinical trial register entries and found that all 440 registered trial records with recruitment status ‘in progress’ that were either non- or partially funded by industry named the scientific leadership of the trial, compared with 49% (111/226) of those funded by industry; findings confirmed by the current study.

There are well-established ethical, scientific and legal obligations associated with being a clinical trial investigator. International research standards such as the International Conference on Harmonization (ICH) Topic E6 require investigators to have appropriate qualifications and experience, to ensure compliance with the trial protocol, to obtain and document informed consent, and to be responsible for the medical care of trial subjects and for the integrity of the research data and results. Although key international standards (ICH E6, Declaration of Helsinki) do not specifically require trials to have named scientific leadership, it seems reasonable to ask for them to be publicly named and accountable for the trials onto which they recruit participants, considering their responsibilities both to the participants they recruit, and to future patients who may benefit from the results of the study. Similarly, it is important that investigators be contactable should the publication of the results of their research be delayed (or not achieved, despite increasing public and legal pressure to do so), to enable the results of studies to be made available to investigators of similar studies and meta-analysts. The PI is also ultimately responsible for registering the trial and hence for the quality of the registered data. Some of the problems identified with the quality of registered data may therefore be solved by having a named PI in the registry record.

Arguably the two most important pieces of information about a clinical trial that need to be registered are the description of the interventions being compared, and the outcomes upon
which any conclusion about the safety and effectiveness of the interventions will be made. As demonstrated by this and previous studies, the quality of this information, as it has been registered to date, has been poor.27–36

In 2005, nine to ten percent of registered trial records on ClinicalTrials.gov provided an incomplete or nonspecific description of the intervention name.30,31 Although subsequent studies suggest that this has improved to less than two or three percent,12,14,41 more information is required about the intervention than the name. There should also be a description that is detailed enough for it to be possible to distinguish between the arms of the study. For trials of drugs, biologicals and vaccines this means information on the dose, frequency, route of administration and duration of treatment.25,47 In the current study less than half of the intervention arms where this information was relevant provided it. That there is room for improvement is confirmed by the fact that records of some trials (Phase 0 and I) describe interventions in greater detail, perhaps due to a greater focus on the specifics of the intervention in these trials.

Similarly, more is required when registering trial outcomes than the name. To be complete the record should contain the name of the outcome, information on the instrument that is being used to measure it (when applicable), and the time points at which it will be measured. Primary outcomes with a specific measure and a meaningful time frame were registered in only 31% of records evaluated by Zarins et al in 2005, and in 38% of records in the current study.19 Given the critical importance of the primary outcome to the scientific integrity of the study it is of enormous concern that this key information is still not being made public in a way that is meaningful or informative. Since the primary outcome is the one that the study should be designed to evaluate, and hence used to calculate the sample size, it is also concerning that so many trials claim to have multiple primary outcomes with almost one in ten trials claiming four or more. The combined problem of multiple primary outcomes, lack of specification of the instrument being used to measure the outcome, and non-reporting of time frames leaves the door open for fishing expeditions and will not solve the problem of selective reporting bias.

The trial records in this study were registered between June 2008 and June 2009 on any one of the nine registries that provided data to the ICTRP Search Portal, including ClinicalTrials.gov. Although the latter is the most established and clearly the largest registry, 14% of the records in this study were provided by the other registries. As more countries seek to improve the transparency of clinical trial research involving nationals of that country, to be more accountable to the individuals who consent to participate in clinical research, to better oversee and monitor that research, and to make information accessible in the languages spoken by the nationals of each country, it is inevitable that the number of trial registries will increase.44 Since the start of this study, the number of registries that provide data to the ICTRP has already risen from nine to twelve.

Prospective registration is defined by the ICMJE and WHO as registration of a clinical trial before recruitment of the first participant. Even allowing amnesty for trials registered in compliance with national laws (such as the Food and Drug Administration Amendments Act in the US), more than 40% of the records in our sample were registered one month or more after recruitment of the first participant, with a median time to registration of 10 months for retrospectively registered trials. Data from the Australian New Zealand Clinical Trials Registry (ANZCTR) confirm these findings and show no improvement for 2010 (Personal communication, L. Askie, 29 June 2010). This delay is clearly not acceptable, particularly as many trials could feasibly complete recruitment in such a time frame and could potentially then retrospectively register the trial in a way that could favour a particular result. It is for this reason that some registries refuse to retrospectively register trials. Adoption and enforcement of the ICMJE policy on prospective registration by more journal editors could make an important difference, and some key journals are playing a leading role in this regard.26 By emphasizing the importance of informative entries and specifically underlining the consequences of omitting information, journal editors could contribute even more to the attainment of high-quality registration.

It is important to note that any study of the quality of registered records is not the same as a study of the quality of the design or conduct of clinical trials. It is just as possible that the trials that have not been adequately registered are of high quality as low quality. However, just as the quality of a trial and its results can usually only be assessed against the quality of the publication reporting those results, in the absence of the complete protocol we have no other choice than to judge the quality of a trial’s design against the information entered into a trial registry.

It has now been five years since the ICMJE and the World Health Assembly put their crucial support behind the need to prospectively register clinical trials. In the time that has passed the number of registered trials has increased from less than 10,000 to more than 120,000, but a significant proportion of the information that has been registered remains deficient. In an attempt to improve the quality of registered data the WHO ICTRP has introduced a number of measures. One is to improve the explanatory text for the Trial Registration Data Set to make the requirements for registration clearer, particularly for contact, intervention and outcome information.21 Another is the establishment of International Standards for Clinical Trial Registries, the aim of which is to improve the quality of registered data by establishing a clear minimum requirement for quality control processes performed and data recording practices used by individual clinical trial registries. It is our intention to repeat this study following...
the introduction of the standards and continue to monitor the quality of registered data. If successful, these measures could improve the meaningfulness and usefulness of registered data, and hence ensure its scientific, ethical and moral integrity.

ACKNOWLEDGEMENTS

We wish to thank Ghassan Karam for his help in attaining a random sample of registered records from the ICTRP database. Additionally, we are grateful to Dr Bianca de Stavola from the London School of Hygiene and Tropical Medicine, for her advice regarding methods of statistical analysis for clustered data sets.

REFERENCES

The quality of registration of clinical trials


The quality of registration of clinical trials: still a problem

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The quality of registration of clinical trials: still a problem.
ABSTRACT
Introduction
The benefits of clinical trials registration include improved transparency on clinical trials for healthcare workers and patients, increased accountability of trialists, the potential to address publication bias and selective reporting and possibilities for research collaboration and prioritization. However, poor quality of information in registered records of trials has been found to undermine these benefits in the past. Several years have now passed since the nascent of clinical trial registration. Trialists’ increasing experience with trial registration and recent developments in registration systems may have positively affected data quality. This study was conducted to investigate whether the quality of registration has improved, or whether it is a more persistent problem.

Methods
We repeated a study from 2009, using the same methods and the same research team. A random sample of 400 records of clinical trials that were registered between 01/01/2012 and 01/01/2013 was taken from the International Clinical Trials Registry Platform (ICTRP) and assessed for the quality of information on 1) contact details, 2) interventions and 3) primary outcomes. Results were compared to the equivalent assessments from our previous study.

Results
The number of records that provided a name of a contact person increased from 81.0% in to 85.5% and the number of records that provided either an email address or a telephone number increased from 68.7% to 74.9%. The number of intervention arms that were complete in registering intervention specifics increased from 44.2% to 51.9%. The number of primary outcomes that were specific measures with a meaningful timeframe increased from 38.2% to 57.6%. Approximately half of all trials continued to be retrospectively registered.

Discussion
There have been small but significant improvements in the quality of registration since 2009. However, significant problems with quality remain and continue to constitute an impediment to the meaningful utilization of registered trial information.

INTRODUCTION
Clinical trials registration is now broadly considered an ethical and scientific responsibility. In the past fifteen years, national and regional trial registries have been established in Africa, Asia, Australia/Oceania, Europe, North America and South America. The WHO International Clinical Trials Registry Platform (ICTRP) was established in 2005 with the aim of bringing registered trial data from different trial registries together and creating a single point of access to information on all clinical trials conducted globally. It now combines data from 15 national and regional clinical trial registries, offering access to data from more than 200,000 trials.

There are important advantages to the increased transparency on clinical trial conduct and reporting brought about by these developments. It improves access to information on clinical trials for healthcare workers, researchers and patients; it allows for steps to be taken against publication bias and selective reporting; it carries the potential to increase the accountability of those conducting clinical trial research; and it makes the identification of gaps in the health research landscape possible, thus facilitating priority setting in research.

The degree to which registered trial data can be used for these purposes depends on the completeness and meaningfulness of the data registered. The quality of data in registered records has been shown to be poor in the past. However, clinical trials registration has matured in recent years. Trialists may have gotten better at registering. Moreover, registries are likely to have improved their registration systems after the implementation of the International Standards for Clinical Trial Registries in 2010.

This study was conducted to investigate whether the poor quality of registration observed in the past has been due to trial registration being in its nascence, or whether it is a more persistent problem. To do so, we repeated a study conducted by us in 2009, using the same methods and the same research team.

METHODS
A random sample of 400 registered records of clinical trials that were registered between 1 January 2012 and 1 January 2013 was taken from the ICTRP database. Records of trials that were registered as having an observational study design were not eligible for the sample. For trials that were registered in more than one registry (duplicate records), only the record with the earliest registration date was considered eligible. At the time the sample was taken the database included trials registered in fifteen different registries.
The quality of registration of clinical trials: still a problem

Sample size calculation
With a sample size of 380 records, all upper and lower 95% confidence intervals for extrapolation to the entire ICTRP dataset, calculated using the Wilson score interval (see further under analysis), would deviate 5% at most from the estimated number. A sample size of 380 also fulfilled this study’s requirements to detect relatively minor changes in the quality of the three primary outcomes: the quality of contact details, interventions and outcomes (minor changes were defined as a 10% increase or decrease in the proportion of adequately registered records). It allowed for detecting an increase or decrease of 10% (using two-tailed test and α=0.05) with β>0.85 in the quality of contact details and interventions and with β>0.95 in the quality of primary outcomes. In our previous study in 2009, 3% of trials were incorrectly registered as interventional. Therefore, a final sample size of 400 records was chosen to allow for exclusion of these trials.

Data extraction
Registry name, trial ID, target sample size, inclusion criteria for gender and age of participants, recruitment status, date of registration, date of first enrolment and the public and scientific title for each record were downloaded from the ICTRP database and imported into Excel on 13 February 2013.

Records of trials that were registered as interventional but were in fact records of observational trials, diagnostic accuracy trials or treatment protocols for continuation of treatment after inclusion in a study protocol were excluded from further data extraction.

Descriptive information on study design was extracted manually from the complete registered record in the source registry. Data on interventions and sponsorship was also extracted manually and was then coded. The system used to code interventions was adapted from the codes used for intervention types on ClinicalTrials.gov. Primary sponsors were coded as being foundation, government, industry, university/hospital, or other. Trials were coded as being industry funded (primary sponsor was industry), partially industry funded (primary sponsor was non-industry, but secondary sponsor or source of monetary or material support was industry) or non-industry funded.

Outcome measures
The number of primary outcomes per record was collected. Each primary outcome was evaluated for specificity, using a classification system adapted from the system used by Zarin et al in their assessment of quality of outcomes. If a record contained multiple outcomes, all were assessed separately. Outcomes were classified as being a specific measure, a domain, vague, an unexplained abbreviation, or a part of safety monitoring. Besides assessing the specificity of each outcome, the presence or absence of a time frame was collected for every outcome. Some outcomes assessed the duration of an event, the time to an event or were safety monitoring outcomes. For these outcomes, reporting a time frame is not possible, and the timeframe was therefore denoted as irrelevant. Time frames were denoted to be not meaningful when they did not specify a point in time when the outcome was to be measured.

Only outcomes mentioned in the outcome fields were assessed. Other texts in the record were scanned for additional information on mentioned outcomes. To assess the overall completeness of registration of intervention specifics, a binary outcome variable was used that could be incomplete versus complete registration of the intervention. Complete registration entailed the reporting of drug name, dose, duration, frequency and route.

Contact information
The presence or absence of the following contact details was evaluated: name of a contact person (investigator or other), email address and telephone number. The WHO 20-item Trial Registration Data Set requires registration of separate scientific and public contact details. There was, however, variation in registration formats for contact details between different registries. Some registries had one field for contact details, others had two separate fields for public and scientific contact details and others multiple contact fields. For records with only one contact field the presence of contact information was extracted from that field. For records with multiple contact fields, if the contact details were present in any of the fields, the information was denoted to be present.

Interventions
Given the considerable variability in the types of interventions evaluated in trials, comparison of registration quality between different intervention categories is difficult. Therefore, the evaluation of the quality of registered intervention data was limited to trials that investigated drugs, biologicals or vaccines, including active comparators. Placebo comparators were not evaluated. For each intervention and active comparator the presence or absence of the following five intervention specifics was collected: name, dose, duration of the intervention, frequency of administration and route of administration. All intervention arms were assessed separately. Name was denoted to be present if a company serial number or a drug name was provided. Only interventions and active comparators mentioned in the intervention field were assessed. Other texts in the record were scanned for additional information on mentioned interventions. To assess the overall completeness of registration of intervention specifics, a binary outcome variable was used that could be incomplete versus complete registration of the intervention. Complete registration entailed the reporting of drug name, dose, duration, frequency and route.
Internal inconsistency in study design
Internal inconsistencies in study design fields were identified.44 Internal inconsistencies were defined as records with multiple descriptors that were not compatible, such as ‘single-group’ and ‘controlled or randomized’, ‘open-label’ and ‘blinded’, and ‘double-blinded’ without subject or investigator blinding.

Assessment rules
The assessment rules and methods for data extraction for this study are analogous with the rules and methods used in our previous study on the quality of registration.2 As then, all records were assessed for eligibility by RV who then extracted and coded the data. A more detailed overview of the rules used in all assessments is provided in the supporting file that accompanies our previous publication.5

Analysis
95% confidence intervals (CI) were calculated for proportions in the samples using continuity corrected Wilson score intervals with Singleton et al. adjustments for finite populations. These 95% CIs reflect the confidence with which these proportions, measured in our samples of records, predict true proportions in the overall populations of all interventional trials on the ICTRP. The quality of registration was compared between trials registered between 17 June 2008 and 17 June 20092 and trial registered between 1 January 2012 and 1 January 2013 using the Newcombe-Wilson test with continuity correction.45–47

Statistical analyses were performed using MS Excel.

RESULTS
A sample of 400 records was taken from a total of 23,046 unique interventional trials that were registered between 1 January 2012 and 1 January 2013.14 records were excluded from data extraction because the corresponding trials were of an observational or diagnostic accuracy study design or were a treatment protocol for continuation of treatment after inclusion in a study protocol. A total of 386 records was included for data extraction, of which 221 (57.3% [52.2%-62.2%]) investigated drugs, biologicals or vaccines (Figure 11.1).

All information that had to be extracted manually from the registered records was collected between 13 February 2013 and 23 February 2013. Baseline data on registry name, primary sponsor category, intervention type, study phase, study design, randomization status and inclusion criteria for gender of participants are presented in Table 11.1.
### Table 11.1. General descriptive information

<table>
<thead>
<tr>
<th>Registry name</th>
<th>2009</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of records</td>
<td>Percentage of records (%)</td>
<td>Number of records</td>
</tr>
<tr>
<td>ClinicalTrials.gov</td>
<td>628</td>
<td>65.9 (83.2-88.3)</td>
</tr>
<tr>
<td>JPRN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IRCT</td>
<td>4</td>
<td>0.5 (0.2-1.5)</td>
</tr>
<tr>
<td>ANZCTR</td>
<td>26</td>
<td>3.6 (2.4-5.2)</td>
</tr>
<tr>
<td>EU-CTR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ISRCTN</td>
<td>39</td>
<td>5.3 (3.9-7.3)</td>
</tr>
<tr>
<td>ChiCTR</td>
<td>11</td>
<td>1.5 (0.8-2.7)</td>
</tr>
<tr>
<td>CTRI</td>
<td>4</td>
<td>0.5 (0.2-1.5)</td>
</tr>
<tr>
<td>DRKS</td>
<td>2</td>
<td>0.3 (0.0-1.1)</td>
</tr>
<tr>
<td>NTR</td>
<td>16</td>
<td>2.2 (1.3-3.6)</td>
</tr>
<tr>
<td>CRIS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PACTR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RPCEC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SLCTR</td>
<td>1</td>
<td>0.1 (0.0-0.9)</td>
</tr>
<tr>
<td>ReBec</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Primary sponsor

- **Foundation**: 10 (1.4 [0.7-2.6])
- **Government**: 39 (5.3 [3.9-7.3])
- **Industry**: 246 (33.7 [30.3-37.2])
- **University / hospital**: 398 (54.4 [50.8-58.0])
- **Other**: 37 (5.1 [3.7-6.9])
- **Not specified**: 1 (0.1 [0.0-0.9])

#### Intervention type

- **Drug**: 385 (52.7 [49.0-56.3])
- **Biological / vaccine**: 82 (11.2 [9.1-13.7])
- **Device**: 49 (6.7 [5.1-8.8])
- **Procedure / surgery**: 69 (9.4 [7.5-11.8])
- **Radiation**: 23 (3.1 [2.1-4.7])
- **Behavioural**: 76 (10.4 [8.4-12.9])

Notes:
- The number of registries that provide data to the ICTRP has increased from nine to fifteen in between 2009 and 2013. Registry acronyms stand for: ClinicalTrials.gov (CT.gov), Japan Primary Registries Network (JPRN), Iranian...
The quality of registration of clinical trials: still a problem

Records were additionally checked for the presence of entries in the fields for recruitment status, date of first enrolment and the public and scientific title. The former three were present in all records, the latter was reported in 379 records 98.2% [96.1%-99.2%], which constituted a significant improvement from the observed 95.8% in 2009. Furthermore, information was collected on sample size and age of participants. Sample size was reported in 384 records (99.5% [97.9%-99.9%]), which was not statistically different from the observed 98.6% in 2009. The median target sample size was 77 [IQR 39 – 200]. Age of participants was reported in 375 records (97.2% [94.8%-98.5%]), which was not statistically different from the observed 98.6% in 2009. The median of this difference was 2 months. The registration date was in an earlier month than the date of first enrolment in 125 records (32.4% [27.8%-37.3%]). The median of this difference was 2 months. The registration date and date of first enrolment were in the same month in 76 records (19.7% [15.9%-24.1%]).

The presence of study phase in records was analysed separately for trials in drugs, biologicals or vaccines. Of 439 trials researching these types of interventions, study phase was reported in 370 records (84.9%). Of 221 trials researching these types of interventions, study phase was reported in 172 records (77.8%).

Quality of registration of contact information

Overall, 330 records reported a name of a contact person (85.5% [81.5%-88.8%]). 259 records provided an email address (67.1% [62.2%-71.7%]) and 272 records a telephone number (70.5% [65.6%-74.9%]). 289 records provided either an email address or a telephone number (74.9% [70.2%-79.0%]). These constituted significant improvements with regard to 2009 for the presence of an email address, the presence of a telephone number and the presence of either (Table 11.2). Improvement in the presence of a name of a contact person was not significant. All changes for the subcategories of industry, non-industry and partially industry sponsored records were not significant.

The presence of contact details was disaggregated according to trials’ recruitment status (Table 11.3). The presence of names of contact persons did not differ markedly for trials with a different recruitment status, but email addresses, telephone numbers or either were present more frequently among recruiting or not yet recruiting trials than among completed trials, especially for industry sponsored trials.

Quality of registration of interventions involving drugs, biologicals or vaccines

There were 221 records of trials that investigated drugs, biologicals or vaccines. These reported 351 experimental or active comparator arms (Table 11.4). Completeness of registration of the name of the intervention, the duration of the intervention, the frequency of administration and the route of administration did not significantly change between 2009 and 2013. Information on the dose was present significantly more often in 2013 than in 2009. 182 arms (51.9% [46.5%-57.1%]) were complete in registering intervention specifics, which also constituted a significant improvement from the observed 44.2% in 2009.

Quality of registration of outcome measures

The 386 included trial records reported 705 primary outcomes. 261 records (67.6% [62.7%-72.2%]) reported one primary outcome, 62 (16.1% [12.6%-20.2%]) reported two, 29 (7.5% [5.2%-10.7%]) reported three and 32 (8.3% [5.8%-11.6%]) reported four or more. The maximum number of primary outcomes reported in one record was 52. Two records (0.5% [0.1%-2.1%]) reported no primary outcome at all.

The degree of specificity of reported outcomes was assessed (Table 11.5). To prevent skewing the data, the outcomes in the record with 52 outcomes were counted as one for this analysis (the 2nd highest number of outcomes in any record was 12). 377 primary outcomes (57.6% [53.8%-61.4%]) were specific measures for which a meaningful time frame was present or for which a time frame was irrelevant. This constituted a significant improvement from the observed 38.2% in 2009.

Internal inconsistencies in study design

Internal inconsistencies in the study design fields were encountered in 10 records (2.6% [1.3%-4.9%]). This was a significant improvement from the observed 9.3% in 2009.
Table 11.2.
The presence of contact details in registered records in 2009 and 2013

<table>
<thead>
<tr>
<th>SPONSORSHIP</th>
<th>YEAR</th>
<th>N</th>
<th>NAME (%)</th>
<th>EMAIL (%)</th>
<th>TELEPHONE NR. (%)</th>
<th>EMAIL OR TEL. NR. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>2009</td>
<td>246</td>
<td>53.7 [47.3-59.9]</td>
<td>39.0 [33.0-45.4]</td>
<td>46.7 [40.5-53.1]</td>
<td>56.5 [50.1-62.7]</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>97</td>
<td>53.6 [43.3-63.6]</td>
<td>47.4 [37.3-57.7]</td>
<td>57.7 [47.3-67.5]</td>
<td>61.9 [51.4-71.3]</td>
</tr>
<tr>
<td>Partially industry</td>
<td>2009</td>
<td>76</td>
<td>97.4 [90.1-99.5]</td>
<td>63.2 [51.4-73.6]</td>
<td>65.8 [54.1-75.9]</td>
<td>65.8 [54.1-75.9]</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>25</td>
<td>96.0 [77.8-99.8]</td>
<td>72.0 [50.5-87.1]</td>
<td>84.0 [63.2-94.7]</td>
<td>84.0 [63.2-94.7]</td>
</tr>
<tr>
<td>Non-industry</td>
<td>2009</td>
<td>408</td>
<td>94.4 [91.6-96.3]</td>
<td>70.8 [66.2-75.1]</td>
<td>74.3 [69.7-78.3]</td>
<td>76.5 [72.1-80.4]</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>261</td>
<td>96.2 [92.9-98.0]</td>
<td>73.6 [67.7-78.7]</td>
<td>78.0 [73.0-83.2]</td>
<td>78.0 [73.0-83.2]</td>
</tr>
<tr>
<td>Overall</td>
<td>2009</td>
<td>731</td>
<td>81.0 [78.0-83.7]</td>
<td>59.4 [55.7-62.9]*</td>
<td>64.2 [60.6-67.8]*</td>
<td>68.7 [65.2-72.0]*</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>386</td>
<td>85.5 [81.5-88.8]</td>
<td>67.3 [62.2-71.7]*</td>
<td>70.5 [65.5-74.9]*</td>
<td>74.9 [70.2-79.0]*</td>
</tr>
</tbody>
</table>

Notes: Percentages of records for which different aspects of contact details were present in 2009 and 2013. * = significant difference between 2009 and 2013.

Table 11.3.
The presence of contact details according to recruitment status for trials registered between 1 January 2012 and 1 January 2013

<table>
<thead>
<tr>
<th>SPONSORSHIP</th>
<th>RECRUITMENT STATUS</th>
<th>N</th>
<th>NAME (%)</th>
<th>EMAIL (%)</th>
<th>TELEPHONE NR. (%)</th>
<th>EMAIL OR TEL. NR. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>Not yet recruiting</td>
<td>10</td>
<td>80.0 [44.4-96.4]</td>
<td>80.0 [44.4-96.4]</td>
<td>70.0 [35.5-91.8]</td>
<td>80.0 [44.4-96.4]</td>
</tr>
<tr>
<td></td>
<td>Recruiting</td>
<td>51</td>
<td>47.1 [33.2-61.1]</td>
<td>66.7 [52.0-78.8]</td>
<td>84.3 [70.9-92.5]</td>
<td>90.2 [77.9-96.3]</td>
</tr>
<tr>
<td></td>
<td>Completed or stopped</td>
<td>36</td>
<td>55.6 [38.4-71.6]</td>
<td>11.1 [3.6-26.9]</td>
<td>16.7 [7.0-33.4]</td>
<td>16.7 [7.0-33.4]</td>
</tr>
<tr>
<td>Partially industry</td>
<td>Not yet recruiting</td>
<td>9</td>
<td>100.0 [61.1-100.0]</td>
<td>100.0 [61.1-100.0]</td>
<td>100.0 [61.1-100.0]</td>
<td>100.0 [61.1-100.0]</td>
</tr>
<tr>
<td></td>
<td>Recruiting</td>
<td>13</td>
<td>100.0 [71.8-100.0]</td>
<td>61.5 [32.4-84.8]</td>
<td>84.6 [53.8-97.3]</td>
<td>84.6 [53.8-97.3]</td>
</tr>
<tr>
<td></td>
<td>Completed or stopped</td>
<td>3</td>
<td>66.7 [12.7-98.2]</td>
<td>33.3 [1.8-87.3]</td>
<td>33.3 [1.8-87.3]</td>
<td>33.3 [1.8-87.3]</td>
</tr>
<tr>
<td>Non-industry</td>
<td>Not yet recruiting</td>
<td>51</td>
<td>100.0 [91.3-100.0]</td>
<td>88.2 [75.5-95.1]</td>
<td>94.1 [82.8-98.5]</td>
<td>96.1 [85.5-99.3]</td>
</tr>
<tr>
<td></td>
<td>Recruiting</td>
<td>144</td>
<td>95.1 [89.9-97.8]</td>
<td>79.2 [71.5-85.3]</td>
<td>85.4 [78.4-90.5]</td>
<td>85.4 [78.4-90.5]</td>
</tr>
<tr>
<td></td>
<td>Completed or stopped</td>
<td>66</td>
<td>95.5 [86.5-98.8]</td>
<td>50.0 [37.6-62.4]</td>
<td>45.5 [33.4-58.1]</td>
<td>50.0 [37.6-62.4]</td>
</tr>
<tr>
<td>Overall</td>
<td>Not yet recruiting</td>
<td>70</td>
<td>97.1 [89.2-99.5]</td>
<td>88.6 [78.2-94.6]</td>
<td>91.4 [81.7-96.5]</td>
<td>94.3 [85.9-98.1]</td>
</tr>
<tr>
<td></td>
<td>Recruiting</td>
<td>208</td>
<td>83.7 [77.8-88.2]</td>
<td>75.0 [68.5-80.6]</td>
<td>80.8 [74.6-87.5]</td>
<td>86.5 [81.0-90.7]</td>
</tr>
<tr>
<td></td>
<td>Completed or stopped</td>
<td>105</td>
<td>81.0 [71.9-87.7]</td>
<td>36.2 [27.2-46.2]</td>
<td>35.2 [26.4-45.2]</td>
<td>38.1 [29.0-48.1]</td>
</tr>
</tbody>
</table>

Notes: Percentages of records for which different aspects of contact details were present for recruiting and non-recruiting trials.

Table 11.4.
The completeness of intervention specifics in registered records in 2009 and 2013

<table>
<thead>
<tr>
<th>YEAR</th>
<th>N</th>
<th>NAME (%)</th>
<th>DOSE (%)</th>
<th>DURATION (%)</th>
<th>FREQUENCY (%)</th>
<th>ROUTE (%)</th>
<th>ALL COMPLETE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>726</td>
<td>98.2 [96.9-99.0]</td>
<td>70.5 [67.1-73.8]*</td>
<td>70.0 [66.5-73.2]</td>
<td>75.8 [72.5-78.8]</td>
<td>73.7 [70.3-76.8]</td>
<td>44.2 [40.6-47.9]*</td>
</tr>
<tr>
<td>2013</td>
<td>351</td>
<td>94.6 [94.0-98.1]</td>
<td>77.5 [72.7-81.7]*</td>
<td>68.9 [63.8-73.7]</td>
<td>73.2 [68.2-77.7]</td>
<td>79.2 [74.5-83.2]</td>
<td>51.9 [46.5-57.1]*</td>
</tr>
</tbody>
</table>

Notes: Percentages of total number of intervention (and active comparator) arms for which different intervention specifics were present in 2009 and 2013. * = significant difference between 2009 and 2013.
### Table 11.5.
Degree of specificity of primary outcomes in 2009 and 2013

<table>
<thead>
<tr>
<th>Classification (%)</th>
<th>Examples</th>
<th>2009 (N=1271)</th>
<th>2013 (N=654)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific measure</strong></td>
<td>All-cause mortality, quality of life by SF-36, pulmonary functioning by FEV-1</td>
<td>47.1 [44.4-49.9]*</td>
<td>69.1 [65.4-72.6]*</td>
</tr>
<tr>
<td><strong>Domain</strong></td>
<td>Freedom from progression, quality of life, pulmonary functioning</td>
<td>36.7 [34.1-39.4]*</td>
<td>21.1 [18.1-24.5]*</td>
</tr>
<tr>
<td><strong>Vague</strong></td>
<td>Efficacy, symptoms, laboratory parameters</td>
<td>5.4 [4.3-6.8]*</td>
<td>3.2 [2.1-4.9]*</td>
</tr>
<tr>
<td><strong>Unexplained abbreviation</strong></td>
<td>Any unexplained abbreviation</td>
<td>3.5 [2.6-4.6]*</td>
<td>1.2 [0.6-2.5]*</td>
</tr>
<tr>
<td><strong>Safety monitoring</strong></td>
<td>Adverse event monitoring, drug toxicities, complications</td>
<td>7.3 [6.0-8.9]</td>
<td>5.4 [3.8-7.4]</td>
</tr>
<tr>
<td><strong>Time (%)</strong></td>
<td>Mortality at one year, ECG twice a year, social impact throughout study</td>
<td>Time present</td>
<td>65.9 [63.3-68.5]</td>
</tr>
<tr>
<td>Time present, not meaningful</td>
<td>10.8 [9.2-12.6]</td>
<td>7.6 [5.8-10.0]</td>
<td></td>
</tr>
<tr>
<td>Time absent</td>
<td>7.7 [6.3-9.3]</td>
<td>13.8 [11.3-16.7]</td>
<td></td>
</tr>
<tr>
<td>Time irrelevant</td>
<td>15.6 [13.7-17.7]</td>
<td>15.3 [12.7-18.3]</td>
<td></td>
</tr>
</tbody>
</table>

Notes: The specificity and presence of a time frame for primary outcomes, presented as percentages of the total number of primary outcomes in 2009 and 2013. * = significant difference between 2009 and 2013.

### Table 11.6.
The quality of information on contact details, interventions and primary outcomes per registry for trials registered between 1 January 2012 and 1 January 2013

<table>
<thead>
<tr>
<th>Registry name</th>
<th>Contact details</th>
<th>Intervention</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name present (%)</td>
<td>Email or tel. nr. present (%)</td>
<td>All intervention specifics complete (%)</td>
</tr>
<tr>
<td>ClinicalTrials.gov</td>
<td>83.8 [78.1-88.2]</td>
<td>68.9 [62.4-74.8]</td>
<td>54.0 [46.9-61.1]</td>
</tr>
<tr>
<td>JPRN</td>
<td>91.2 [75.3-97.7]</td>
<td>58.8 [40.9-74.8]</td>
<td>17.6 [7.4-35.1]</td>
</tr>
<tr>
<td>IRCT</td>
<td>100.0 [86.4-100.0]</td>
<td>100.0 [86.4-100.0]</td>
<td>65.6 [46.9-80.8]</td>
</tr>
<tr>
<td>ANZCTR</td>
<td>100.0 [80.9-100.0]</td>
<td>100.0 [80.9-100.0]</td>
<td>100.0 [73.4-100.0]</td>
</tr>
<tr>
<td>EU-CTR</td>
<td>19.0 [6.3-42.5]</td>
<td>85.7 [62.8-96.2]</td>
<td>14.3 [4.7-33.5]</td>
</tr>
<tr>
<td>ISRCTN</td>
<td>100.0 [772-100.0]</td>
<td>58.8 [33.6-80.5]</td>
<td>-</td>
</tr>
<tr>
<td>ChiCTR</td>
<td>100.0 [73.4-100.0]</td>
<td>100.0 [73.4-100.0]</td>
<td>0.0 [0.0-34.2]</td>
</tr>
<tr>
<td>CTRI</td>
<td>100.0 [68.1-100.0]</td>
<td>100.0 [68.1-100.0]</td>
<td>95.0 [73.2-99.7]</td>
</tr>
<tr>
<td>DRKS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NTR</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CRIS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PACTR</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RPCEC</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Notes: * Less than 10 records, arms or outcomes.
The quality of registration of clinical trials: still a problem

Table 11.7. Data recording formats for the three primary outcomes of this study (contact information, intervention specifics and outcome quality) at the registries that provided data to the ICTRP at the time of the study in 2013

<table>
<thead>
<tr>
<th>Data recording formats</th>
<th>Number of registries for which each question is</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contacts</strong></td>
<td></td>
</tr>
<tr>
<td>Are there separate fields for scientific and public inquiries?</td>
<td>true 12, false 5, 70.6% 29.4%</td>
</tr>
<tr>
<td>Are there separate fields for different contact details?</td>
<td>true 17, false 0, 100.0% 0.0%</td>
</tr>
<tr>
<td>And if so, a field for the name of the contact person?</td>
<td>true 17, false 0, 100.0% 0.0%</td>
</tr>
<tr>
<td>a telephone number?</td>
<td>true 15, false 2, 88.2% 11.8%</td>
</tr>
<tr>
<td>an email address?</td>
<td>true 16, false 1, 94.1% 5.9%</td>
</tr>
<tr>
<td>Is there a separate field for the Principal Investigator?</td>
<td>true 8, false 9, 47.1% 52.9%</td>
</tr>
<tr>
<td>Is there a separate field for the person updating data?</td>
<td>true 3, false 14, 17.6% 82.4%</td>
</tr>
<tr>
<td>Is there a separate field for the person that registered?</td>
<td>true 2, false 15, 11.8% 88.2%</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Are interventions categorized (e.g. drug, surgery, behavioural, etc.)?</td>
<td>true 9, false 8, 52.9% 47.1%</td>
</tr>
<tr>
<td>Are there separate fields for separate arms?</td>
<td>true 12, false 5, 70.6% 29.4%</td>
</tr>
<tr>
<td>Does the intervention field contain specific sub-fields for different aspects of interventions? And if so, a sub-field for arm label and/or description?</td>
<td>true 10, false 7, 58.8% 41.2%</td>
</tr>
<tr>
<td>arm sample size?</td>
<td>true 3, false 7, 30.0% 70.0%</td>
</tr>
<tr>
<td>arm type (intervention, active comparator, placebo)?</td>
<td>true 9, false 1, 90.0% 10.0%</td>
</tr>
<tr>
<td>dose?</td>
<td>true 4, false 6, 40.0% 60.0%</td>
</tr>
<tr>
<td>duration of the intervention?</td>
<td>true 2, false 8, 20.0% 80.0%</td>
</tr>
<tr>
<td>frequency of administration?</td>
<td>true 1, false 9, 10.0% 90.0%</td>
</tr>
<tr>
<td>route of administration?</td>
<td>true 3, false 7, 30.0% 70.0%</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Are there separate fields for primary and secondary outcomes?</td>
<td>true 16, false 1, 94.1% 5.9%</td>
</tr>
<tr>
<td>Are outcomes categorized (e.g. safety, efficacy)?</td>
<td>true 2, false 15, 11.8% 88.2%</td>
</tr>
<tr>
<td>Does the outcome field contain specific sub-fields for different aspects of outcomes? And if so, a sub-field for name?</td>
<td>true 11, false 6, 64.7% 35.3%</td>
</tr>
<tr>
<td>time point?</td>
<td>true 11, false 0, 100.0% 0.0%</td>
</tr>
<tr>
<td>method of measurement / measure specification?</td>
<td>true 2, false 9, 18.2% 81.8%</td>
</tr>
</tbody>
</table>

Notes: There is information on 17 registries in this table, instead of 15, because the JPRN registry is in fact a registry network that consists of three registries that all provide data to the WHO ICTRP. Each of these was assessed separately.

**DISCUSSION**

A persistent problem

This study was conducted using the same methods and the same research team as our previous study on the quality of registration. There have been small but significant improvements in the quality of registration since 2009. However, significant problems with quality remain and continue to constitute an impediment to the meaningful utilization of registered trial information.
The quality of registration of clinical trials: still a problem

There have been small improvements to the presence of contact details overall. This is partially due to the larger proportion of non-industry trials in the analysis of trials registered in 2012, which do better on registering contact details. But across all sponsor categories quality also improved, the main exception being the continued lack of mentioning of names of contact persons by industry sponsors. Explicit mentioning of the name of the principal investigator is important to increase the accountability of trialists. Furthermore, despite improvements, contact information such as a telephone number or email address often remain absent. Remarkably trialists appear to remove contact details when trials have been completed or stopped, in particular for industry sponsored trials. To allow patients, healthcare workers and other researchers to inform themselves of clinical trials, it is important that trialists can be contacted at any stage of a trial. Such information should remain available after a trial is completed or stopped.

There was some improvement in the completeness of intervention specifics for drug trials, however, the improvement was minor. Contrariwise, the improvement in the quality of registered outcomes was marked. This is a hopeful development for systematic reviewers, since in the absence of a complete trial protocol, registered clinical trial data constitute the only way to identify selective reporting. However, specific information about the outcome in registered records is necessary to detect selective outcome reporting as part of systematic reviews, and still almost half of the number of outcomes do not constitute a specific measure with a meaningful timeframe. Moreover, it has been proposed that the specificity of outcomes should be assessed at a greater level of granularity, to take into account more subtle forms of selective reporting.

In conclusion, there have been small improvements to the quality of registered trial data, but poor quality is a persistent problem. Recent publications have also shown concomitant results reporting at individual registries to be problematically incomplete, such as at ClinicalTrials.gov, despite legal obligations in the US to report the findings of trials.

The causes of poor quality (and learning from other registries)
The persistent nature of poor quality of registered clinical trial data suggests one or more pervasive causes. Although trialists themselves have a responsibility to ensure that the information in registered records is complete and accurate, registries can encourage high-quality registration through quality control processes and appropriate data recording practises. Both are addressed in the International Standards for Clinical Trial Registries.

Our analysis suggests that there are important differences between registries with regard to registration quality. Notably, there are few that score bad on all three aspects of quality that we tested, or good on all. Rather, there are differences depending on which aspect is assessed. These differences might at least be partially explained by varying data recording formats.

For example, some registries specifically ask trialists for the methods of measurement for each outcome. Others have only free text fields for outcomes. Some registries ask for specific details on interventions, others, again, have only free text fields. Some registries ask trialists to categorize interventions and outcomes, others do not. For data quality and data aggregation purposes, it is important that discrete options are offered where there is a limited set of possible answers (supplemented by a free text field to allow for additional explanation where needed), that different sub-aspects of data set items are specifically queried (Table 11.7), and that the data recording formats are harmonized across all individual registries.

The differences in the quality of registration of different data items found in this study suggest that registries can learn from each other. Differences between registries in terms of data recording practices and their consequences for data quality deserve to be studied in more detail. With regard to quality control, too, registries could learn from each other in terms of what information is considered mandatory and a precondition for registration, and which different tiers of data checking (e.g. automated checks and manual checks) can be implemented to detect incomplete or non-meaningful entries. The International Standards for Clinical Trial Registries state that benchmarking of registries should be one of the next steps in standards development for registries.

Enforcement
To be able to make use of the potential benefits that clinical trials registration offers, it is of paramount importance that registration is complete and accurate. However, it must also be comprehensive. Enforcement of clinical trials registration has increased substantially over the past decade, owing to national legislation on registration, policies by journal editors and publishers making registration a prerequisite for publication, ethics committees and national research ethics oversight agencies requiring registration as part of procedures for ethics approval, policies by funders making registration a prerequisite for grant approval, codes of research practice that recommend trial registration, such as the SPIRIT 2013 and CONSORT 2010 statements which include sections recommending the admission of trial registration details to both clinical trial protocols and reports, statements from professional organizations such as the declaration of Helsinki, and self-regulation by universities and the pharmaceutical industry. Despite these measures, a proportion of trials currently remains unregistered, especially in countries lacking legislation on trial registration.

National legislation is crucial in enforcing the registration of all clinical trials. Several of the other enforcement measures outlined above have been instrumental in creating momentum for clinical trials registration, such as journal and ethics review board requirements for
The quality of registration of clinical trials: still a problem

The quality of registration of clinical trials: still a problem

registration, yet not all journal editors require registration as a pre-condition for publication, not all clinical trials are conducted with the goal of publication, and not all ethics committees have policies on clinical trials registration in place. Therefore, it is imperative that all countries that have not implemented legislation on trial registration do so. Furthermore, it is important that the remit of legislation on registration should cover all possible clinical trials, as is being recognized in the US and the EU. Currently, in those countries where legislation to enforce registration is present, its remit is often limited to a sub-set of trials.

Therefore, it is imperative that all countries that have not implemented legislation on trial registration do so. Furthermore, it is important that the remit of legislation on registration should cover all possible clinical trials, as is being recognized in the US and the EU. Currently, in those countries where legislation to enforce registration is present, its remit is often limited to a sub-set of trials.

With regard to enforcement, the commitment of the pharmaceutical industry to clinical trials registration is important and the past development of a Joint Position of several pharmaceutical associations on the disclosure of clinical trial information via clinical trial registries and databases is laudable. However, the Joint Position needs revisiting on two important aspects. First, currently, it allows for registration after commencement of patient enrolment and allows trialists to withhold data specified by the WHO Minimum Trial Registration Data Set if they consider it sensitive – both of which are in contradiction with policies on clinical trial registration by WHO and the International Committee of Medical Journal Editors (ICMJE). Second, the Joint Position mentions that ‘registration of clinical trials on any one of a number of free, publicly accessible, internet-based registries should achieve the intended objectives’. To ensure the quality of registered trial data, the WHO ICTRP search portal only provides access to data from trials registered at registries that meet certain quality standards (excluding, for example, registries managed by for-profit agencies). To realize a single point of access to all clinical trial data conducted globally, it is important that the pharmaceutical associations include a commitment to registration in WHO approved registries in the next update of their Joint Position, as the ICMJE already has. Finally, enforcement of trial registration by the pharmaceutical industry would be further advanced if support for clinical trials registration and results reporting would not be limited to statements from the pharmaceutical associations, but if more individual pharmaceutical companies would subscribe to the AllTrials campaign, following the example of GlaxoSmithKline.

Besides increasing the number of trials that is registered, enforcing measures could also help improve the quality of registration. Journal editors, for example, have been called upon to not only enforce registration itself, but to also implement quality control procedures. Although editors have made clear that trial registration with missing or uninformative fields for the minimum data elements is inadequate, little is known about to what degree journals are putting such measures into practice. Similarly, both in the EU and in the US legislature supports the WHO Minimum Trial Registration Data Set – the minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered. Failure to comply with registration legislation may result in penalties or withholding of federal grants. Yet, little is known to what extent legislators are planning to invoke such measures, and whether the quality of registration could play a role in such decisions. For both legislators and journal editors discussion needs to be initiated on how far measures should go to discourage incomplete or inadequate registration. This applies to both the initial registration of a clinical trial, which was the subject of this study, as for results reporting in registry databases.

CONCLUSION

There have been small but significant improvements in the quality of registration since 2009. However, significant problems with quality remain and continue to constitute an impediment to the meaningful utilization of registered trial information. More effort needs to be made to improve data recording formats, enhance quality control measures and scale up enforcement of trial registration.

ACKNOWLEDGEMENTS

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The quality of registration of clinical trials: still a problem

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Information on blinding in registered records of clinical trials

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Information on blinding in registered records of clinical trials.
ABSTRACT
Information on blinding is part of the data that should be provided upon registration of a trial at a clinical trials registry. Reporting of blinding is often absent or of low quality in published articles of clinical trials. This study researched the presence and quality of information on blinding in registered records of clinical trials and highlights the important role of data-recording formats at clinical trial registries in ensuring high-quality registration.

BACKGROUND
The International Clinical Trials Registry Platform (ICTRP) at the World Health Organization (WHO) provides a single point of access to information on more than 200,000 clinical trials made available by registries around the world. To set a standard for the quality of entries in registered records, the WHO Trial Registration Data Set was established, defining the minimum amount of trial information that must appear in a record. Part of the information that is required on study design consists of information on whether blinding was used and, if so, who was blinded.

We recently reported on the quality of information in a random sample of registered records of clinical trials taken from the ICTRP. In this report, we outline the inconsistencies that we encountered in the use of blinding terminology and highlight the important role of data-recording formats in attaining high-quality trial registration.

FINDINGS
Our previous study analysed 731 registered records of clinical trials that were registered between 17 June 2008 and 17 June 2009 at one of nine clinical trial registries around the world. This sample was acquired by taking a random 5% sample from the ICTRP database. We report here on the same sample, with the exception that single-arm trials were excluded because they lacked relevance to blinding. The presence and quality of information on blinding was assessed for 571 records.

For each registered record we denoted: 1) whether there was information on blinding in the registered record; 2) whether the record reported a blinding label and if so, what the blinding label was; and 3) whether the record mentioned who was blinded in the trial, and if so, which groups of individuals were blinded.

Of the 571 records in our study sample, 43 (8%) did not contain any information on blinding, and 212 records (37%) were of trials where there was no blinding (open-label). Of the 316 records (55%) that reported that participants were blinded as part of the trial, 48 records (15%) reported only blinding labels (single-blind, double-blind), 8 (3%) contained information only on who was blinded, and 260 (82%) reported both.

For the 260 records for which both blinding labels and information on who was blinded were present, blinding labels were cross-tabulated with who was blinded (Table 12.1). Data-recording formats for blinding varied across the registries (Figure 12.1). Records from one of the three registries with free text fields for blinding or study design were less likely to
contain any information on blinding, compared with registries that requested information on who was blinded or that requested a blinding label (OR = 23, 95% CI: 11 - 48, χ² = 123, P<0.001). Records from one of the three registries that specifically asked for information on who was blinded were more likely to contain this information, compared with records from registries that only asked for a blinding label or had a free-text field for blinding or study design (OR = 719, 95% CI: 91 - 5664, χ² = 205, P<0.001).

Table 12.1. Trialists’ interpretations of the terms ‘single-blind’ and ‘double-blind’

<table>
<thead>
<tr>
<th>WHO WAS MENTIONED AS BLINDED</th>
<th>SINGLE-BLIND</th>
<th>DOUBLE-BLIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient, caregiver, data analyst / investigator, outcomes assessor</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>Patient, caregiver, data analyst / investigator</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Patient, caregiver, outcomes assessor</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Patient, data analyst / investigator, outcomes assessor</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Caregiver, data analyst / investigator, outcomes assessor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Data analyst / investigator, outcomes assessor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Patient, outcomes assessor</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Patient, data analyst / investigator</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>Patient, caregiver</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Outcomes assessor</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Data analyst / investigator</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Caregiver</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patient</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>194</td>
</tr>
</tbody>
</table>

Notes: Records that contained both blinding labels and information on who was blinded mainly originated from two registries. One registry asked for information on the blinding status of subjects, clinicians or therapists, outcome assessors and/or data analysts. The other registry asked for information on the blinding status of subjects, caregivers, outcome assessors and/or investigators. Because of the similarity between these two classifications, for this table, trials that were labelled to the fourth category of ‘data analysts’ on one registry and ‘investigators’ on the other were categorized as the same group.

Figure 12.1. Data recording formats for information on blinding at the nine registries

Notes: Three registries requested information on who was blinded by asking for the blinding status of specific groups of individuals. The groups of individuals about which information was requested differed per registry.

- Subject
- Clinician or therapist
- Outcomes assessor
- Data analyst

- Subject
- Caregiver
- Investigator
- Outcomes assessor

- Participant
- Investigator
- Outcome assessor
- Data-entry operator/statistician

- One registry requested both information on groups and a blinding label.
DISCUSSION
Information on blinding is often not provided in published articles of clinical trials, and many trials remain unpublished. Clinical trial protocols offer the most complete resource of information on the study design of trials. Given the current absence of open access to clinical trial protocols, the only other source of information on study design that is publicly available is the registered record of the trial. It is therefore important that information on blinding can be found in the study-design descriptions of registered records of trials. This study shows that this is not always the case. In addition, the sole use of the terms ‘single blinding’ and ‘double blinding’ was found to be common, despite the lack of clarity on their exact meaning. It is a confirmation that these labels should not be used alone, but should be accompanied by information on who was blinded.

Until recently, the groups of individuals that can potentially introduce a bias into a trial through knowledge of treatment assignments were not clearly defined. The groups on which the registries in our study requested information were not consistent (Figure 12.1). The 2010 revision to the Consolidated Standards of Reporting Trials (CONSORT) statement has created considerable clarity on this issue by defining five possible groups of people that can be blinded in a trial: participants, healthcare providers, data collectors, outcome adjudicators, and data analysts (See Additional File 1, taken from the CONSORT 2010 statement). The widespread use of these definitions by clinical trial registries would improve the quality and interpretability of information on blinding across clinical trial records from different registries.

More generally, our findings confirm the pivotal role for data recording formats at clinical trial registries in attaining high-quality information in registered records of clinical trials. The ICTR has recognized this and has recently initiated the establishment of International Standards for Clinical Trial Registries. The aim of these standards is to improve the quality of registered data by establishing a minimum requirement for quality control processes performed and data recording practices used by individual clinical trial registries. It is important that the quality of registered trial information continues to be monitored, especially after the introduction of these standards.

ADDITIONAL FILE 1
Item 11a of the CONSORT 2010 statement reads: ‘Box 4, on blinding terminology, defines the groups of individuals (that is, participants, healthcare providers, data collectors, outcome adjudicators, and data analysts) who can potentially introduce bias into a trial through knowledge of the treatment assignments.’ This additional file was not admitted to this thesis but is available at: http://www.trialsjournal.com/content/13/1/210/additional
13
Discussion
CONTRIBUTIONS OF THE THESIS

This thesis makes contributions to the evidence base for global health research and development (R&D) governance in several areas. By examining health research priority setting processes at the global level and investigating good practices for such processes – the first objective of this thesis – it contributes to methods development in the area of global health research prioritization. Global-level health research priority setting processes have not been the subject of much inquiry in the past. By presenting an analysis of all priority setting processes that were organized or coordinated through the World Health Organization (WHO) over a period of five years, this thesis shows that these processes are currently of variable quality. Subsequently, the thesis presents work that aims to help address this problem in the form of the checklist for health research priority setting. Since its development, the checklist has proven its value in a considerable number of health research prioritization exercises (e.g. 2–12). The most important contribution of the checklist is that it helps those who conduct a health research priority setting exercise not to overlook important aspects of the process.

By exploring how data on currently ongoing health R&D can inform health research priority setting processes – the second objective of this thesis – the thesis addresses the need for a better information base for health research priority setting processes. First, the thesis presents a comprehensive mapping of currently available health R&D data that was developed through a collaborative effort of several researchers. The mapping constitutes an important first step in assessing how global health R&D monitoring could be improved. After this, the thesis focuses specifically on investigating the strengths and limitations of one potential new data source on global health R&D: registered clinical trial data. Two case studies are presented that provide analyses of data from the WHO International Clinical Trials Registry Platform (ICTRP), currently the most comprehensive database of registered clinical trials. One case study with a broad scope is described, showing that registered trial data can be used to acquire broad insight into the health R&D that is currently being conducted in the world – information with the potential to inform high-level policy directions for health R&D. Another case study with a narrow scope is described, showing that registered trial data can also be used to acquire more precise and specific insights into ongoing health R&D in more defined research areas (such as pharmacokinetic research for paediatric populations) – information with the potential to inform lower-level decisions about R&D priorities for specific health problems, interventions or populations.

Through the two case studies, the thesis demonstrates that utilizing registered clinical trial data to monitor health R&D has four strengths:

- Completeness: All trials should be registered even if the final result of a trial is not published, making registries of clinical trials, in particular the ICTRP, the most complete resource of information on the global distribution of clinical trial research.
• Up-to-date insight: Databases of registered trials can provide insight into currently ongoing research. This allows for up-to-date evaluation of previously established priorities.16
• Searchability: The standardized and searchable format of registered records makes databases of registered trials suitable for aggregate analysis.17
• Complementary information: Registered records contain information that is complementary to information in published articles.18

Besides assessing the strengths of utilizing registered clinical trial data to inform priority setting processes, the thesis also evaluates the barriers that currently prevent the meaningful utilization of these data—the third objective of this thesis. Three main barriers are identified. The first is comprised by the lack of enforcement of trial registration. Enforcement has increased substantially over the past decade, yet in many countries, and particularly in low- and middle-income countries, legislation on registration remains absent.19 Although there are many other enforcement measures, without legislation, we cannot be sure that all trials are registered.20 Indeed, research has shown that currently not all trials are registered.20-24 Hence, completeness is currently simultaneously a strength and a weakness of clinical trials registration—the ICTRP is the most complete resource of information on the global distribution of clinical trial research, but it is not complete enough. The second barrier is that extracting, aggregating, and analyzing registered trial data from the ICTRP currently requires significant manual labour. Further automation of aggregation and analysis, and the subsequent public disclosure of the results of that analysis, would be an important step forward for the ICTRP and for clinical trial transparency globally.25,26 The third key barrier to the meaningful utilization of registered clinical trial data is the poor quality of data in registered records. This barrier is explored in detail in this thesis. It is shown that to improve that quality, data recording formats and quality control measures at individual registries need to be improved. Hence, two conclusions can be drawn from this thesis about the utilization of registered clinical trial data in health research priority setting processes:

1. Registered clinical trial data constitute a valuable resource for assessing the global distribution of clinical trials and for informing policy development for health R&D.
2. To increase the usefulness of registered clinical trial data further, it is important that the enforcement of clinical trial registration be increased, that more possibilities for automated aggregate data analysis on the ICTRP be created, and that the quality of data in registered records be improved.

Taking all investigations together, the thesis also allows for several broader conclusions to be drawn with regard to global health R&D governance. Recently, the director of research and evidence of the UK Department for International Development (DFID) stated with regard to health research that ‘prioritizing research areas is an art, not a science’.27 This thesis argues that the opposite is true—prioritizing research areas is a science, not an art. It shows that rigorous methods are available to establish high-quality health research priority setting processes at the global level, but that these methods are currently underused. It demonstrates that the information needed to appropriately prioritize the areas of greatest health R&D need is obtainable, but not systematically collected. Finally, it makes clear that there is an urgent need for greater collaboration in addressing global priorities for health research, but that such coordination currently only takes place on an ad-hoc basis in selected areas. These are missed opportunities to ameliorate the mismatch between the health R&D that is needed and the R&D that is undertaken.

LIMITATIONS OF THE THESIS
There are several important limitations to this thesis.

First, the checklist for health research priority setting that is presented in this thesis is a high-level, generic guidance document. For each of the themes of good practice on the checklist separate reviews and methodological research studies are conceivable. The development of the checklist should be viewed as a starting point for discussion on how health research priority setting exercises should be conducted, not an end point.

Second, the thesis has only explored how information on currently ongoing health R&D can inform health research priority setting processes. As explained in the Introduction, there is another key information gap with regard to global-level health research priority setting: the lack of a systematic mechanism for assessing the need for new knowledge and/or products at the global level. The thesis does not present any inquiry into how such needs assessments should be conducted.

Third, within this thesis’s investigations of how data on currently ongoing health R&D can inform health research priority setting processes, the focus lay on one area—the investigation of how registered clinical trial data can be utilized in such processes. However, there is more to health R&D than just clinical trials. Considerable advancements remain to be made in the utilization of other information resources, such as research investments, for global health R&D monitoring.14-18 This thesis presents an overview of the different available information sources and their limitations, but has not explored the strengths and limitations of other information resources in detail.

Fourth, the case studies that were conducted to investigate the utilization of registered clinical trial data for monitoring global health R&D also have their limitations. These studies were primarily proof-of-principle studies intended to highlight how registered clinical trial data may be used to identify gaps in the health R&D landscape. In doing so, the case studies
Discussion

Overview of the recent developments and current policy context in this area.

Health R&D. This section discusses what will be needed to realize this, and provides a succinct essence, is a more coordinated approach to prioritizing, funding and conducting health research that will be required to address the mismatch. What is needed, in essence, is a more coordinated approach to prioritizing, funding and conducting health R&D – a supplementary global system that can facilitate a more needs-driven approach to health R&D. This section discusses what will be needed to realize this, and provides a succinct overview of the recent developments and current policy context in this area.

Recent Developments and Next Steps in Global Health R&D Governance

This thesis has explored global-level priority setting processes for health research. The rationale for these investigations was that there is a mismatch between the health R&D that is needed and the R&D that is in fact undertaken (see Chapter 2). However, priority setting is only one component of global health R&D governance, and this thesis’s recommendations for improving health research priority setting processes constitute only one part of the broader set of solutions that will be required to address the mismatch. What is needed, in essence, is a more coordinated approach to prioritizing, funding and conducting health R&D – a supplementary global system that can facilitate a more needs-driven approach to health R&D. This section discusses what will be needed to realize this, and provides a succinct overview of the recent developments and current policy context in this area.

Over the years, there have been several expert committees that have suggested solutions to the mismatch.13–36 The most recent in this line of committees was the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG),37 an expert committee established by the World Health Assembly in 2010. The CEWG released an extensive report in 2012, which provides recommendations for how to systematically identify global health R&D priorities and ensure that these are addressed in a coordinated manner. The starting point for realizing this is described to be the establishment of a Global Observatory on Health R&D.41,51

The mission of an Observatory is envisioned to include the mapping of health R&D needs, with the goal of establishing clarity on R&D priorities (‘best buys’40), and the bringing together of health R&D funders to facilitate coordinated action on a shared R&D agenda. If these goals are to be reached, lessons would have to be learned from the shortfalls of the Global Forum for Health Research, an organization with a similar mandate which was recently discontinued. Two lessons are of particular importance to the challenges that an Observatory could be faced with. First, although the Global Forum established a process for continuous monitoring of global investments in health R&D,37 it never succeeded in conducting a comprehensive mapping of the needs for new knowledge and/or products. Arguably, this is the most important step of any priority setting process for health R&D and would need to be a focus of an Observatory.42 Second, the most effective way to ensure that ‘best buys’ in health R&D are indeed funded, would be to link an Observatory to a pooled funding mechanism, akin to the Global Health Research Fund once suggested by the Commission on Macroeconomics and Health.38 Such a fund could disperse funding to public, private or public-private partnership research entities in areas of identified priority health R&D need.51 Should this prove unfeasible, then an alternative would be to bring together funders of health R&D to galvanize coordinated action on a shared R&D agenda.39,40,51 The Global Forum was established precisely to be a forum for such discussion, but never succeeded in actually bringing funders together to discuss ‘best buys’ in health R&D. To prevent a similar course of events with an Observatory, it will be essential to generate broad support for this new platform and to work together with key funders of health R&D in giving rise to the final shape and form of an Observatory.41 One way to do this would be to learn or even build from existing models of funder collaboration that have proven to be successful, such as the European and Developing Countries Clinical Trials Partnership (EDCTP)42 and ESSENCE on Health Research.43

Strengthening national health research systems, in particular in those countries with the largest burden of disease, was already noted as being of particular importance to correcting the 10/90-gap in 1990 by the Commission on Health Research for Development.35 Their report lead to the establishment of the Council on Health Research for Development (COHRED) in 1993, an organization whose mission is to improve health, equity and development by
supporting countries to develop strong research and innovation systems. Yet, two decades later, despite significant efforts to improve countries’ health research systems, by COHRED and others, this still constitutes a challenge of pressing priority. An envisaged additional advantage of an Observatory would be that it could provide an impetus for national health research system strengthening. It could do so by stimulating the development of good practices and standards in health research, by providing support for building capacity for health R&D in developing countries, by producing analyses to inform national R&D portfolio management, and by creating a platform to convene stakeholders.

The pharmaceutical industry has developed more expertise with technologies for the conversion of basic scientific discoveries into new therapies than the public sector and the involvement of the for-profit private sector is thus of major importance in creating solutions to the mismatch. Many different approaches for engaging the for-profit private sector in targeting unprofitable R&D and for delinking the price of health R&D from its cost have been proposed and tested in recent years. Examples are product development partnerships (PDPs), which have proven particularly effective for developing new products for neglected diseases, other public-private partnerships (PPPs), such as those recently announced by both the EU and the US that will aim to develop new antibiotics in the face of increasing antibiotic resistance; economic incentives established through legislation, which have shown to be effective for stimulating R&D for paediatric medicines and orphan drugs (although only in part, with both orphan drugs and paediatric medicines concerns have been raised about using economic incentives, since the R&D that is stimulated through such measures remains driven by market incentives rather than by need), and different kinds of prizes and grants to companies, which are considered to be particularly effective for stimulating health R&D of relevance to developing countries.

Besides improving the prioritization of health R&D needs, facilitating the coordination of public and philanthropic funders, strengthening national health research systems, and engaging the for-profit private sector, it will be necessary to increase access to research results and to improve research collaboration (through open approaches to R&D, equitable licensing and patent pools).

Finally, there is a need to gather these different measures under the umbrella of a concerted mechanism through the establishment of a global framework or convention on health R&D (WHO has the option to create legally binding conventions on the basis of a two-thirds majority vote of its Member States, but has only done so once). A framework or convention would provide the global governance framework to secure the nature of health R&D as a global public good, making explicit the globally-shared responsibilities for addressing global health R&D needs and thus raising the financial resources needed to realize such sizeable changes to the global health R&D system. Notably, such funds would allow for the realization of a pooled funding mechanism linked to an Observatory, providing an effective, coordinated and sustainable source of funding for identified health R&D priorities. The establishment of a framework or convention has been a much discussed topic in recent years. Since countries would be expected to contribute financially based on their level of development, while the R&D output would mainly benefit populations in developing countries, it has been a much contested proposal on which nations have stood divided.

At the most recent World Health Assembly of May 2013, discussion on a framework or convention was postponed till 2016. This is a regrettable outcome after more than two decades of negotiations and reports by several expert working groups, who have all made sensible and rational suggestions to improve the world’s health R&D system, but have been met with little action.

Although discussion on a framework or convention was postponed, the establishment of a Global Observatory on Health R&D was enacted at the most recent World Health Assembly. Furthermore, WHO was requested to review possibilities for coordinating and financing global health R&D priorities and to facilitate the implementation of several health R&D demonstration projects to address identified gaps that disproportionately affect developing countries. These plans alone are not enough to address the substantive mismatch between the health R&D that is needed and that which is undertaken. Still, they constitute an important step forward and, looking ahead to the World Health Assembly in 2016, present an opportunity for demonstrating the value of more far-reaching changes to the global governance framework for health R&D. It is important that WHO takes immediate action to demonstrate that value, in particular through coordinating the selection and implementation of the health R&D demonstration projects.

**RECOMMENDATIONS FOR FUTURE RESEARCH**

To support the development of policies and practices for a global health R&D system that is more responsive to the world’s health needs, research is needed on how health research priorities can be established as part of a Global Observatory on Health R&D in a feasible, fair and legitimate way, and on what opportunities exist for increasing coordination in addressing those priorities, both in terms of funding and conducting the research. This section describes these research needs in more detail.

As part of the envisioned Global Observatory on Health R&D, processes for global-level health research priority setting will need to be reviewed and reassessed. A particular challenge is the comprehensive nature of priority setting on this scale. There have been global-level health research priority setting exercises that encompassed all areas of health in the past, but
these have all been singular exercises and have all approached priority setting in different ways. The establishment of an Observatory will require assessment of the appropriateness of previous processes and the development of a consensus approach.

Additionally, good priority setting starts with good information, and to support the development of priority setting processes as part of an Observatory, it will be necessary to explore how the information that these processes are based on can be improved. As explained in the Introduction, there are three main sources of information for health research priority setting processes:

- Information on the magnitude and distribution of existing health problems
- Information on the need for new knowledge and/or products to address those problems
- Information on the health R&D that is already being undertaken

Research is needed on how the need for new knowledge and/or products can be assessed on a global scale. There is, for example, currently no agreed approach for comparing R&D needs between different health areas. Particularly how such needs assessments could be conducted systematically and periodically, yet feasibly, will require inquiry. This is an area of research that should be addressed with priority, since it will constitute an important component of an Observatory, yet past experiences from the Global Forum for Health Research have shown that it is a difficult mechanism to establish.

Furthermore, only by comparing the health R&D that is needed with the health R&D that is currently being conducted, can inferences be made about how our priorities for health R&D should change. All information sources on health R&D that are currently available have substantial limitations, in particular with regard to data from low- and middle-income countries. Hence, there is a need for investigation of how global health R&D monitoring could be improved. With regard to the utilization of registered clinical trial data for global health R&D monitoring, this thesis has shown that improvements are needed to the enforcement of registration, the possibilities for automated aggregate data analysis on the ICTRP, and the quality of registration. To enable such improvements, research is needed in particular on the degree of current enforcement of clinical trials registration, especially in countries that lack legislation on registration. Innovative research designs will need to be used to quantify how many trials currently remain unregistered and to advocate for the implementation of legislation where it currently remains absent. The knowledge needed to implement automated aggregate data analysis on the ICTRP is largely available, and does not constitute a research need. To improve the quality of registration, action is needed by registries in improving data recording formats and quality control mechanisms. Research focused on how differences in these two registry functions influence the quality of registration could further assist registries in learning from each other.

Finally, there is an urgent need for greater coordination on global health R&D priorities, in particular by key funders of health R&D. Yet, what opportunities exist for realizing such increased coordination in practice is unclear. More research in this area is required. There needs to be more clarity on what the remits are of the largest public and philanthropic funders of health R&D, to whom they are accountable, and what the consequences of these remits and accountabilities are for their ability to collaborate in addressing shared health R&D priorities. More work is needed on what these funders fund, both collectively and individually – work that is currently hampered by a lack of transparency by funders on the health R&D that they fund, as well as by the kaleidoscope of different research classification mechanisms that funders apply to categorize their research funding to health areas and research types. It will be important to involve funders in these investigations, and inquire how they themselves view their responsibilities to address a global health R&D agenda, and what opportunities and challenges they see for increasing coordination amongst each other on such an agenda. Furthermore, although there have been numerous investigations into approaches for engaging the private sector in targeting unprofitable R&D and for delinking the price of health R&D from its cost, many of these approaches are still in their infancy, and others are only partial solutions. It is important that we continue to assess what can be learned from current and past collaborations aimed at addressing priority health R&D needs.
REFERENCES


DS
Dutch summary | Samenvatting
DE DISCREPANTIE TUSSEN HET GEZONDHEIDSONDERZOEK DAT NODIG IS EN HET GEZONDHEIDSONDERZOEK DAT WORDT UITGEVOERD

Elk jaar wordt er wereldwijd ongeveer 240 miljard dollar uitgegeven aan gezondheidsonderzoek. Dit onderzoek heeft de afgelopen eeuw geresulteerd in kennis en producten welke veel levens hebben gered. Echter, door de manier waarop gezondheidsonderzoek wordt gefinancierd en uitgevoerd, zijn er tevens onderzoeksbereiken onderbelicht gebleven. De discrepantie tussen het gezondheidsonderzoek dat nodig is en het gezondheidsonderzoek dat wordt uitgevoerd is een van de meest prangende problemen in de mondiale publieke gezondheidszorg.

Een belangrijke uiting hiervan is het weinige gezondheidsonderzoek dat gedaan wordt naar ziektes die vooral voorkomen in lage-inkomenslanden. Echter, het probleem is groter dan dit. De discrepantie is ook relevant voor hoge-inkomenslanden, zoals blijkt uit het weinige onderzoek naar nieuwe antibiotica en geschikte medicijnen voor kinderen. Daarnaast krijgen sommige gezondheidsproblemen wat betreft onderzoek meer aandacht dan andere gezondheidsproblemen, zowel in lage- als in hoge-inkomenslanden.

Er zijn verschillende oorzaken van deze discrepantie: gezondheidsonderzoek is onderhevig aan marktbelangen in het bedrijfsleven; nationale en mondiale prioriteiten voor gezondheidsonderzoek stemmen vaak niet overeen; het toewijzen van financiering voor gezondheidsonderzoek door publieke en filantropische financiers wordt niet alleen ingegeven door welk onderzoek er nodig is maar ook door andere factoren (bijvoorbeeld de invloed van belangengroepen); er is een gebrek aan samenwerking door publieke en filantropische financiers in het gevolg geven aan mondiale prioriteiten voor gezondheidsonderzoek; en er is op mondiaal niveau een gebrek aan adequate processen voor de prioritering van gezondheidsonderzoek. Dit proefschrift richt zich op de laatstgenoemde oorzaak van de discrepantie. Het analyseert hoe gezondheidsonderzoek op mondiaal niveau wordt geprioriteerd en doet suggesties voor verbetering.

PROBLEMEN MET DE PRIORITERING VAN GEZONDHEIDSONDERZOEK OP MONDIAAL NIVEAU

Prioritering van gezondheidsonderzoek heeft als doel vast te stellen welk onderzoek het grootst mogelijke potentieel voor gezondheidswinst heeft (waarbij gezondheidswinst gemeten kan worden in ziektebelast, maar ook met andere maten, zoals de grootte van gezondheidsverschillen tussen bevolkingsgroepen). Er zijn verschillende problemen met de huidige wijze van prioritering van gezondheidsonderzoek op mondiaal niveau. Ten eerste, er is op dit moment geen systeem om alomvattend (voor alle gezondheidsproblemen en alle landen),
op systematische wijze (door het gebruik van rechtvaardige en legitieme methoden), en peri- odiek vast te stellen welk gezondheidsonderzoek mondiaal het meest urgent is. Ten tweede, de processen die gebruikt worden om onderzoeksrioriteiten te stellen zijn vaak ondermaats. Ten derde, de informatie die nodig is ter onderbouwing van prioriteringsprocessen is vaak niet beschikbaar. Ten vierde, wanneer prioriteiten voor gezondheidsonderzoek worden gesteld is het vaak niet duidelijk hoe gevolg moet worden gegeven aan die prioriteiten, en is het derhalve twijfelachtig of de prioriteiten zullen resulteren in onderzoek.

HET ONTWIKKelen VAN METHOden VOOR de PRIORITERING VAN GEZONDHEIDSONDERZOEK

Dit proefschrift levert een bijdrage aan de ontwikkeling van oplossingen voor deze problemen. Zo wordt de „checklist for health research priority setting“ gepresenteerd. Deze is ontwikkeld op basis van een onderzoek naar de wijze van prioritering bij de Wereldgezondheidsorganisatie, een studie van de literatuur, en interviews met experts. De checklist beschrijft negen thema’s welke overwogen dienen te worden in elk prioriteringsproces voor gezondheidsonderzoek, en helpt onderzoekers en beleidsmakers op de juiste wijze prioriteiten te stellen.

DE BEHOEFTe AAN BETERE INFORMATIE OVER HUIDIG GEZONDHEIDSONDERZOEK

Verder maakt het proefschrift suggesties voor hoe de beschikbaarheid van informatie die nodig is voor de onderbouwing van prioritering verbeterd kan worden. Prioriteiten voor gezondheidsonderzoek worden in de regel gesteld door experts, die hun beslissingen baseren op informatie over welk onderzoek er nodig is, en welk onderzoek er al gedaan wordt. Dit proefschrift richt zich op de laatstgenoemde – informatie over welk gezondheidsonderzoek er al gedaan wordt. Om gedetailleerd inzicht te verkrijgen in wat voor gezondheidsonderzoek er op dit moment wordt gedaan, is het nodig om verschillende informatiebronnen te raadplegen. Zo is informatie nodig over de inputs in gezondheidsonderzoek (zoals investeringen of mankracht), over lopende onderzoeksprojecten (zoals klinische trials), over de outputs van gezondheidsonderzoek (zoals publicaties, patenten of producten), en over de impact van die outputs (bijvoorbeeld op de volksgezondheid of op socioeconomische indicatoren). Alle beschikbare bronnen hebben aanzienlijke beperkingen. Onze kennis over welk onderzoek er gedaan wordt in de wereld, waar er onderzoek gedaan wordt, hoe, en door wie, is beperkt. Dit proefschrift presenteert een inventarisatie van welke informatie over gezondheidsonderzoek er op dit moment beschikbaar is, en welke informatie er mist, en zet zo een eerste stap in het verbeteren van onze kennis over het gezondheidsonderzoek dat op dit moment wordt gedaan.

Tevens presenteert het proefschrift onderzoek naar hoe een relatief nieuw type data – gegevens uit klinische trial registers – gebruikt kan worden in prioriteringsprocessen. De afge- klop tien jaar zijn verscheidene maatregelen genomen om de hoofdonderzoekers van klinische trials ertoe te bewegen hun trials te registreren. Een dergelijke registratie houdt in dat er een identificatienummer aangevraagd wordt voor de klinische trial bij een trial register. Verder dient er informatie over de trial aangeleverd te worden aan het register (zoals over de interventie en de uitkomsten van de trial). Deze informatie wordt vervolgens openbaar gemaakt door het trial register, en doorgegeven aan het ‘International Clinical Trials Registry Platform (ICTRP)’ bij de Wereldgezondheidsorganisatie. Het ICTRP verzamelt de gegevens van vijftien verschillende trial registers en biedt zo één centraal toegangspunt tot de gegevens van klinische trials die wereldwijd geregistreerd zijn. Deze databank kan voor verschillende doeleinden gebruikt worden. Tot op heden zijn met name drie mogelijke doeleinden besproken in de literatuur: het verschaffen van informatie over klinische trials aan behandelaars, onderzoekers en patiënten; het bestrijden van publicatiebias en rapporteringsbias; en het vergroten van de mogelijkheden om (hoofd)onderzoekers van klinische trials ter verantwoording te roepen bij problemen met klinische trials.

Dit proefschrift toont aan dat gegevens uit klinische trial registers tevens gebruikt kunnen worden binnen de prioritering van gezondheidsonderzoek. Het proefschrift presenteert twee casestudy’s die laten zien dat deze gegevens zowel gebruikt kunnen worden om breed inzicht te verschaffen in het gezondheidsonderzoek dat er wereldwijd gedaan wordt, als om precies inzicht te creëren in het onderzoek dat gedaan wordt in specifieke onderzoeksgebieden. Derhalve kunnen de gegevens zowel een rol spelen binnen brede beleidsdiscussies over gezondheidsonderzoek, als helpen te bepalen welk onderzoek er nodig is voor specifieke gezondheidsproblemen. Het gebruik van deze gegevens uit klinische trial registers heeft een aantal voordelen: klinische trial registers zijn de meest complete bron over wat voor klinische trials er mondial uitgevoerd worden; de gegevens zijn actueel, omdat de gegevens worden bijgewerkt door de onderzoekers wanneer er wijzigingen zijn in de status van de trial; doordat de gegevens uit klinische trial registers – gebruikt kan worden in prioriteringsprocessen. De afge- klop tien jaar zijn verscheidene maatregelen genomen om de hoofdonderzoekers van klinische trials ertoe te bewegen hun trials te registreren. Een dergelijke registratie houdt in dat er een identificatienummer aangevraagd wordt voor de klinische trial bij een trial register. Verder dient er informatie over de trial aangeleverd te worden aan het register (zoals over de interventie en de uitkomsten van de trial). Deze informatie wordt vervolgens openbaar gemaakt door het trial register, en doorgegeven aan het ‘International Clinical Trials Registry Platform (ICTRP)’ bij de Wereldgezondheidsorganisatie. Het ICTRP verzamelt de gegevens van vijftien verschillende trial registers en biedt zo één centraal toegangspunt tot de gegevens van klinische trials die wereldwijd geregistreerd zijn. Deze databank kan voor verschillende doeleinden gebruikt worden. Tot op heden zijn met name drie mogelijke doeleinden besproken in de literatuur: het verschaffen van informatie over klinische trials aan behandelaars, onderzoekers en patiënten; het bestrijden van publicatiebias en rapporteringsbias; en het vergroten van de mogelijkheden om (hoofd)onderzoekers van klinische trials ter verantwoording te roepen bij problemen met klinische trials.

Echter, er bestaan ook belemmeringen voor het zinvol gebruik van gegevens uit klinische trial registers. Ten eerste, al zijn klinische trial registers de meest complete bron van informatie over de mondiale distributie van klinische trials, ze zijn niet compleet genoeg. Er zijn nog steeds trials die niet geregistreerd worden. Met name in lage- en middeninkomenslanden zijn er onvoldoende maatregelen genomen om de hoofdonderzoekers van klinische trials erop te wijzen om hun trials te registreren.
trials ertoe te bewegen hun trials te registreren. De tweede belemmering is dat het extra-
eren, aggregeren en analyseren van gegevens van het ICTRP voor een groot gedeelte met
de hand moet worden gedaan en dus veel tijd kost. Het verdient aanbeveling dat het ICTRP
dergelijke data aggregatie en analyse automatisseert, en de resultaten openbaar maakt. De
derde belemmering is dat de kwaliteit van de gegevens uit klinische trial registers vaak
ondermaats is. Dit komt, in ieder geval ten dele, door de wijze waarop klinische trial registers
om de informatie vragen, en door de wijze waarop de registers de kwaliteit van de gege-
vens controleren. Om de bruikbaarheid van de gegevens te vergroten, moeten de registers
deze aspecten van het registratieproces verbeteren.

EEN OBSERVATORIUM VOOR GEZONDHEIDSONDERZOEK
Tijdens de World Health Assembly in mei 2013 is besloten een observatorium voor gezond-
heidsonderzoek op te richten, de ‘Global Observatory on Health Research and Develop-
ment’. Dit betreft een belangrijke ontwikkeling met betrekking tot het onderzoek dat gepre-
senteerd wordt in dit proefschrift. De voornaamste functie van het observatorium zal zijn
om op alomvattend, systematische en periodieke wijze gezondheidsonderzoek mondiaal
te monitoren, en prioriteiten voor de toekomst te stellen. Vanwege die functie zal het obser-
vatorium een belangrijke prikkel leveren voor de verdere ontwikkeling van methoden voor
prioritering van gezondheidsonderzoek en voor het verbeteren van de beschikbaarheid van
informatie die gebruikt kan worden in prioriteringsprocessen.

DE IMPLEMENTATIE VAN MONDIALE PRIORITEITEN
VOOR GEZONDHEIDSONDERZOEK
Tot slot verschaf dit proefschrift een kritische discussie over hoe implementatie van mondiale
prioriteiten voor gezondheidsonderzoek verbeterd kan worden. Om dat te bereiken, dienen
publieke en filantropische financiers van gezondheidsonderzoek beter samen te werken
in het gevolg geven aan mondiale prioriteiten voor gezondheidsonderzoek. Bestaande
samenwerkingsverbanden van financiers zouden hierin het voortouw moeten nemen. De
recente oprichting van een observatorium voor gezondheidsonderzoek biedt een platform
voor dergelijke samenwerking. Echter, de oprichting van een observatorium alleen zal niet
genoeg zijn om ervoor te zorgen dat urgent gezondheidsonderzoek ook wordt uitgevoerd.
Er dienen afspraken te worden gemaakt over hoe gezondheidsonderzoek dat op mondiaal
niveau als een prioriteit wordt aangemerkt gefinancierd moet worden. Tijdens dezelfde
World Health Assembly waarin besloten werd tot de oprichting van een observatorium, kon
geen overeenstemming worden bereikt over dergelijke verdergaande maatregelen. Tijdens
de World Health Assembly van 2016 zullen die maatregelen opnieuw besproken worden.

CONCLUSIE
Dit proefschrift legt uit dat er op dit moment geen systeem is om alomvattend, op systema-
tische wijze en periodiek vast te stellen welk gezondheidsonderzoek mondiaal het meest
urgent is. Het laat zien dat er goede methoden bestaan om op mondiaal niveau gezond-
heidsonderzoek te prioriteren, maar dat dergelijke methoden niet genoeg gebruikt worden.
Het laat tevens zien dat de informatie die nodig is om de juiste manier gezondheidson-
derzoek te prioriteren wel aanwezig is, maar op dit moment niet systematisch verzameld
wordt. Tot slot benadrukt het dat meer samenwerking in het gevolg geven aan mondiale
prioriteiten voor gezondheidsonderzoek gewenst is, maar dat dergelijke samenwerking
op dit moment alleen ad-hoc plaatsvindt in bepaalde onderzoeksgebieden. Het recente
besluit om een observatorium voor gezondheidsonderzoek op te richten zou kunnen
helpen om oplossingen te creëren voor deze problemen. Tot die tijd blijven het gemiste
kansen om de mondiale discrepantie tussen het gezondheidsonderzoek dat nodig is en het
gezondheidsonderzoek dat wordt uitgevoerd te verminderen.
Veel mensen hebben mij geholpen bij de totstandkoming van dit proefschrift. Verschillende (co)promotoren en supervisoren hebben mij begeleid in de diverse onderzoeksprojecten en in het schrijven van de hoofdstukken. Met mijn vrienden en collega’s heb ik veel leuke momenten naast de promotie beleefd, waardoor ik me tijdens mijn werkuren altijd kon concentreren op het werk. De liefde en steun van mijn familie hebben de basis gevormd voor zeer veel dingen in mijn leven, waaronder deze promotie. Ik maak graag van deze gelegenheid gebruik om iedereen te bedanken.

Many people have helped in bringing this thesis to fruition. Several supervisors and bosses have guided me in the research projects and in writing the chapters. With friends and colleagues I have had many joyful moments that were not PhD-related, which made it much easier to focus on my thesis when I needed to. The love and support from my family has given me a foundation for many things, including this PhD. I’d like to take this opportunity to thank everyone.

Prof. dr. van der Velden, beste Koos, ik voel me vereerd dat ik bij jou heb mogen promoveren. Je vakkennis over het Nederlandse public health landschap en de internationale public health zijn ongeëvenaard. Ondanks de vele commissies, onderzoeken en andere activiteiten die je leidt, heb je toch altijd de tijd genomen om in detail mijn hoofdstukken te lezen en becommentarie ren. Bedankt daarvoor! Ik wil je ook bedanken voor je inspanningen om mijn onderzoek onder de aandacht van anderen te brengen, bijvoorbeeld met het interview voor de Vice Versa. Verder vind ik het bijzonder hoe je je als hoogleraar opstelt naar de promovendi. Door de open en niet-hiërarchische sfeer die dat creëerde heb ik me altijd vrij gevoeld om mijn mening te geven. Bedankt voor al je hulp, en voor je vele verhalen en lessen over gezondheidszorg-problemen en -oplossingen in Nederland en daarbuiten. Ik hoop dat we elkaar in de toekomst nog veel zullen spreken.

Prof. dr. Ghersi, dear Davina, it has been a while since we have been able to talk in person, as we are literally on opposite sides of the planet these days. Still, by collaborating on articles, and through your supervision of this thesis, I am still able to benefit from your enormous expertise as a public health researcher. However, the majority of our collaboration dates back to Geneva, where I first started working for you as an intern. From the first moment I arrived, you trusted me with the responsibility over a research project. Afterwards, you gave me my first job as a consultant at WHO, and warmly recommended me for several follow-up positions. You have been a true mentor for me, by supporting me in the first steps of my career, but mainly because there is so much that I have learned from you. You helped me to improve my writing skills. You taught me about ethics, and the importance of having a global view. But the most important thing that I learned from you, is the value of rigour in research. You instilled in me that research has to be transparently reported, and thus has to
be defensible and repeatable. I am deeply grateful to you for your lessons, your tutorial, and your help in advancing my career.

Dr. Baltussen, beste Rob, ik heb een erg goede tijd gehad bij NICHE, jouw onderzoeksgroep. Het is mijn thuis geweest de afgelopen anderhalf jaar. Dat heb ik volledig te danken aan het feit dat je zo warm welkom hebt geheten binnen NICHE. Het heeft me erg geholpen dat ik kon werken omringd door andere promovendi op het gebied van global health. Verder heb ik veel respect voor je ontwikkeld als mijn begeleider in deze promotie. Altijd nam je de tijd om me te ondersteunen met strakke deadlines en het oplossen van problemen die ik had. Je liet me veel zelfstandigheid, wat ik erg op prijs heb geheld, en me vertrouwen gaf in mijn eigen werk. Ook vind ik het bijzonder hoe je op de werkvloer professionaliteit uitstraalt en zich altijd aanpast aan de situatie. Ik heb van je onderwijs en adviezen veel geleerd.

RPC, and in PHI), and all the investigators with whom I have had the pleasure of collaborating throughout the years. There have also been many colleagues that have welcomed me into their departments, joined me in pursuing a PhD, or have worked with me on the research projects. Moreover, I have been able to work in new countries, become more experienced in leading projects, and further develop my research skills. I am very grateful to you for continuing to provide me with these opportunities, and look forward to working with you in the future.

I have been so very lucky over the past years in being able to regularly see many good friends of old, and to meet many new friends. It is important to me that after work I can look forward to dinners, drinks, Skype calls, or other get-togethers. Without these, I would never have been able to finish this thesis. Several people merit specific mentioning. Maaik, Dinette, Rienks, Manuel, Daan en Boov; ik vind het verschrikkelijk gaaf dat wij elkaar nog steeds zo vaak zien (helemaal jou natuurlijk, Roomy!). Dank jullie wel voor alle koffietjes, etentjes, en borrelavonden! Dat er nog veel mogen komen. Jeroen, Thomas, 1000, Koen, Paul, Joost, Beelen, Setse en Wouter, prachtig dat wij elkaar nog steeds veelvuldig zien. De dinsdag is heilig, het weekend ook, en als het aan mij ligt blijft dat zo tot in de eeuwigheid. Eric, Sten, Sanne en Esther, shared interests and similar personalities led us to become close friends in what feels like not more than a few days in Geneva. I enjoy our conversations, especially when they switch instantaneously from casual to very serious and back. Let us keep meeting as much as we possibly can in Geneva, Amsterdam, Nijmegen, London, Tanzania, or whereever else (if possible, at places with black cats and corresponding cheese markets). Eric, especially we have become such good friends in Geneva – I hope that in the future we can continue to join each other on holiday trips around the world! There are many others that I see less often, but who remain or have become important – Erica, Ireen, iedereen van de White House (Ol), van de VLL 102, mijn goudgele vrienden, everyone in Geneva that I have not mentioned yet (Chiv! Elsal! Nina!), mijn nieuwe vrienden in Utrecht (Jan!), all my friends in London, my fellow students from the VU (Katrina, Hang!), my fellow public health enthusiasts who are or were at RIVM, en alle andere vrienden in Utrecht en Amsterdam die ik nog niet genoemd heb.

Throughout the years, there have also been many colleagues that have welcomed me into their departments, joined me in pursuing a PhD, or have worked with me on the research that is presented in this thesis. Everyone at the Radboud University Nijmegen, in particular at NICHE, everyone at LSHTM, and all my former colleagues at WHO (in particular at the ICTRP, in RPC, and in PHI), and all the investigators with whom I have had the pleasure of collaborating on research projects, thank you for your collegiality and the many interesting discussions and debates about public health. Sten, zij verdient natuurlijk een apart bedankje als mijn paranorm. Wat mooi dat we na Genève ook in Nijmegen collega’s hebben kunnen zijn. Bedankt voor al je hulp! Ile, ook jou wil ik hier bedanken voor de goede samenwerking en voor alle tijd die je hebt gestopt in het ontwerpen van dit proefschrift.
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CURRICULUM VITAE

Roderik Floris Viergever was born on 2 March 1983 in Delft, the Netherlands.

Roderik – Rik for short – commenced his studies at Utrecht University in the year 2000. He completed his Bachelor of Science in Physics and Astrophysics in 2004. Following this, he enrolled in a selective medical programme with an increased focus on research training, called the Selective Utrecht Medical Master (SUMMA). He received his Medical Doctorate from SUMMA in 2009. In the same year, he completed a Master of Science in International Public Health at the VU University Amsterdam.

In 2009 and 2010, Rik worked on several topics relating to health research governance for the World Health Organization (WHO) in Geneva. In September 2010, he enrolled in a PhD programme at the London School of Hygiene and Tropical Medicine (LSHTM), studying health care provision for victims of human trafficking. In 2012, he enrolled in a PhD programme at NICHE, the Nijmegen International Center for Health Systems Research and Education, part of the Department of Primary and Community Care of the Radboud University Nijmegen Medical Centre in the Netherlands. The end product of this PhD now lies before you.

Rik enjoys teaching, has published in a variety of basic, clinical and health policy research areas and has conducted consultancy projects for various national and international governmental organizations. He is primarily interested in health policy and systems research, and focuses on issues in health research governance and health care provision for vulnerable populations.
LIST OF PUBLICATIONS BY THE AUTHOR
RELEVANT TO THE THESIS

Peer-reviewed publications
• Viergever RF, Rademaker CMA. Finding better ways to fill gaps in pediatric health research. Pediatrics. In press.
• Viergever RF. The mismatch between the health research and development (R&D) that is needed and the R&D that is undertaken: an overview of the problem, its causes, and solutions. Global Health Action. 2013;6:22450.

Published reports

Correspondence

OTHER PUBLICATIONS IN WHICH WORK FROM THE THESIS IS PRESENTED

OTHER PUBLICATIONS BY THE AUTHOR
• Viergever RF, Berg MJ ten, Solinge WW van, Hoepelman AIM, Gisolf EH. Changes in hematological parameters after switching treatment of HIV-infected patients from zidovudine to abacavir or tenofovir DF. HIV Clinical Trials. 2009;10:125–128.
SUMMARY FOR POLICYMAKERS

INTRODUCTION

One of the most pressing problems in global health is that there is a mismatch between the health research and development (R&D) that is needed and the R&D that is undertaken. One of the causes of this mismatch is a lack of appropriate processes for health research prioritization at the global level. This PhD thesis examines the processes underlying global-level health research prioritization and makes suggestions for improvement.

KEY MESSAGES

• Globally, there is a mismatch between the health R&D that is needed and the R&D that is undertaken.
• This thesis shows that the lack of health research for populations in low-income countries is an important part of this mismatch. However, the mismatch also affects high-income countries. This thesis makes clear, for example, that there are gaps in paediatric research. Another example is the lack of research for new antibiotics.
• One of the causes of the mismatch is the lack of appropriate processes for health research prioritization at the global level.
• Policymakers and researchers should use health research priority setting processes to stimulate urgent health R&D.
• Guidelines for how to establish health research priority setting processes are available, such as the checklist for health research priority setting, which is presented in this thesis (see reference at the end of this summary). This checklist can help to improve the quality of a priority setting process and, as a result, the validity of the established priorities.
• Part of the information that is needed to prioritize research is information on what health R&D is already being undertaken. However, our knowledge of what health R&D is being conducted globally, where it is being conducted, by whom and how, is very limited.
• To increase our knowledge of what health R&D is being conducted globally, we will need to improve the available information on R&D inputs (such as investments towards health R&D), R&D processes (such as clinical trials), and R&D outputs (such as published articles).
• This thesis shows that a database of clinical trials, the International Clinical Trials Registry Platform (ICTRP), is a valuable source of information on the clinical trial research that is conducted in the world. However, it also shows that for the ICTRP to be used to capacity, more clinical trials need to be registered, more possibilities for automated aggregate data analysis on the ICTRP need to be created, and the quality of the clinical trial data needs to be improved.
• In May 2013, the World Health Assembly decided that a Global Observatory on Health R&D should be established. The Observatory will help to increase our knowledge of what health R&D is being undertaken in the world.
• The Observatory also offers promise for providing a global mechanism for setting health research priorities in a comprehensive (for all health problems and all countries), systematic (using fair and legitimate methods), and periodical manner.
• Setting priorities, in itself, will not be enough. To address the mismatch, there is a need for more far-reaching measures, to ensure that the health R&D that is needed the most is also funded and conducted. What is needed, in essence, is a more coordinated, global approach to prioritizing, funding and conducting health R&D.
• More far-reaching measures will be discussed at the World Health Assembly in 2016. Until that time, policymakers and researchers should continue to demonstrate the value of such measures. One way of doing this will be through the health R&D demonstration projects that the World Health Organization (WHO) has been requested to facilitate by the World Health Assembly, which will focus on developing health technologies for diseases that disproportionately affect low-income countries.

RECOMMENDED FURTHER READING

• Veeroprop RF. The mismatch between the health research and development (R&D) that is needed and the R&D that is undertaken: an overview of the problem, its causes, and solutions. Global Health Action. 2013a; 6:22450.

“There is a mismatch between the health R&D that is needed and the R&D that is undertaken.”
INTRODUCTION
The book that you have before you is my PhD thesis. It is about how decisions are made about what health research is most needed (the term ‘priority setting’ is often used to describe these decision-making processes). The thesis focuses on decisions that are taken at the global level. In the thesis, I show that such decisions are not always made in the right way and that we should take a more ‘evidence-based’ approach to priority setting. Here below, I describe what that means and why it is important.

WHY DO WE CONDUCT HEALTH RESEARCH?
There are multiple ways in which we can combat diseases. One way of doing this is to cure people that are ill, for example by giving them medicines, or an operation. Another way is to prevent disease, for example by informing people about the dangers of smoking. A third way of combating diseases is to conduct health research, for example by developing a new medicine or diagnostic, by investigating how many people have a disease, or by investigating the causes of a disease. We conduct health research because it provides health workers (such as doctors, nurses, or psychologists) and health policymakers (such as the people who work in ministries of health) with opportunities to respond better to health problems.

ARE WE DOING THE RIGHT HEALTH RESEARCH?
Every year, approximately 240 billion US dollars are spent globally on health research. That is a lot, but not enough to do all the health research that is possible at the same time. Therefore, researchers and funders of health research have to make choices about what research to do. The problem that this thesis addresses is that when you compare the research that we need, to the research that is conducted, that there is a mismatch. The mismatch means that the research that we need is not always conducted. For example, some areas of health research are neglected, little research is conducted in these areas. That is why it is important to address the mismatch.

WHY IS THERE A MISMATCH?
There are two main causes of the mismatch. About half of all the health research conducted globally is paid for by companies. The goal of these health researchers is to make profit. Unfortunately, the areas in which money is to be made are often not the same as the areas in which research is most needed. As a result, some areas of health research have become neglected.

Another half of all health research is paid for by public funders (governments) and philanthropic organizations (charities and foundations). These funders also contribute to the mismatch, mainly because they do not work together enough in funding the research that is needed the most.

SETTING PRIORITIES
To address the mismatch, it is important to set health research priorities. We set such priorities to identify what health research is most needed. Policymakers and researchers use various criteria to decide what research is most needed. For example, they may prefer to invest in research for a disease that affects a lot of people, in research that has previously been neglected, or in research that will mainly be of benefit to people who are poor. It all depends on what the people who prioritize find important.

**THIS THESIS SHOWS THAT THERE ARE PROBLEMS**
For this thesis, I have researched how health research priorities are set at the global level. In other words, I studied the processes that are used to set priorities. I show that there are two important problems with how health research priorities are set.

1. When you set priorities, it is important that you do this in the right way. We also call this the ‘quality’ of the priority setting process. Many priority setting processes are of low quality. Often, for example, there are no plans for updating the priorities or for turning the priorities into actual research (the risk of this is that the priorities will just be reported as a document and that the prioritized research will never actually be funded). Another example of low quality is that priority setting processes are often not reported transparently.

2. Priorities should be set by experts in a research area. However, those experts need to base their decisions about what health research is most needed on information (such as information on how many people have a disease in different parts of the world, or information on what kind of health research is currently being conducted). That information is often not available. For example, we know very little about what health research is being conducted in the world, who conducts it, where it is conducted, and how. We don’t even know how much money is spent globally on research for individual diseases.

**TAKE HOME MESSAGES**
I hope you will remember the following from reading this summary:

- At a global level, there is a mismatch between the health research that is needed, and the health research that is conducted. The mismatch means that the research that we need is not always conducted. For example, some areas of health research are neglected, little research is conducted in these areas.
- To address the mismatch, it is important to set health research priorities. Priority setting means that we identify what health research is most needed, it is my thesis that we need an evidence-based approach for setting those priorities. This means that it is important to use a high-quality process for setting the priorities, and to collect the right information as part of that process.
- The establishment of the Global Observatory on Health Research is important because this organization will help to identify the health research that is most needed globally.
- There is still no agreement among policymakers about how the research priorities that are identified by the Observatory should be funded.

**SUMMARY FOR ANYONE WHO IS NOT AN EXPERT IN THE FIELD OF HEALTH RESEARCH**

**INTRODUCTION**

**WHY DO WE CONDUCT HEALTH RESEARCH?**

**ARE WE DOING THE RIGHT HEALTH RESEARCH?**

**WHY IS THERE A MISMATCH?**

**SETTING PRIORITIES**

**THIS THESIS SHOWS THAT THERE ARE PROBLEMS**

**TAKE HOME MESSAGES**

**“Priority setting means that we identify what health research is most needed.”**

**THIS THESIS ALSO SUGGESTS IMPROVEMENTS**

In the thesis, I also suggest solutions for these problems. I present the checklist for health research priority setting, which is a document that provides guidance on how to set priorities for health research. It helps researchers and policymakers to establish priority setting processes that are of high quality. Second, I contribute to improving the availability of information on what health research is currently being conducted in the world. I investigate if a new database of clinical trials, the International Clinical Trials Registry Platform (ICTRP), can help to solve this problem (clinical trials are a specific type of health research that is used to test interventions, such as medicines or an operation, on people). I conclude that the ICTRP can help to improve our knowledge of what health research is being conducted in the world. However, I also show that there are still important barriers that need to be overcome, before the ICTRP can reach its full potential.

**RECENT DEVELOPMENTS**

Recently, there has been a development that may help to address the mismatch. A Global Observatory on Health Research will soon be established. The function of this Observatory will be to recommend health research priorities at the global level. This is important, because currently such an organization does not exist. However, setting priorities alone is not enough. After the Observatory identifies research as a priority, that research needs to be funded and conducted. There is no agreement yet among policymakers how this should be achieved. This is something that will need to be clarified in the future.