RAND EUROPE

Impacts of increasing requirements for research and development (R&D) cost transparency

Literature review

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Preface

This report sets out a review of academic and grey literature on the subject of the transparency of the costs of researching and developing new medicines and vaccines. The literature review was undertaken by researchers at RAND Europe, assisted by Dr Jorge Mestre-Ferrandiz (freelance researcher, expert in the field of pharmaceutical industry economics) and Dr Andrew Mulcahy (RAND Corporation).

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Summary

There is controversy around just how costly is the research and development (R&D) entailed in bringing new medicines or vaccines (hereafter collectively referred to as 'medicines') to market. Calls for greater transparency around those costs are heard from policymakers internationally, notably (by implication) in the 2019 World Health Assembly's (WHA) resolution WHA72.8 on 'Improving the transparency of markets for medicines, vaccines, and other health products'[1] and (explicitly) in the European Commission's (EC) 2020 'Pharmaceutical strategy for Europe'[2] and the US Congress's Inflation Reduction Act of 2022[3].

This report presents a literature review undertaken in the autumn of 2022 to discover what that literature says about:

How far and by what methods it is possible to identify, and hence be transparent about, the R&D costs of a new medicine.

What the implications would be, were greater transparency of R&D costs of individual medicines to be achieved, including implications for medicine pricing and innovation.

The R&D cost of a new (successfully launched) medicine has three main elements:

1. 'Out-of-pocket (OOP) costs' of R&D incurred year by year
2. The cost of capital combined with the number of years it takes to bring a new medicine from discovery to being sold on the market for use with patients
3. The 'attrition rate', i.e. the percentage of successful medicines relative to the number researched at the outset.

We carried out a detailed review of both the academic and the grey literature up to August 2022, covering empirical studies estimating the R&D costs of medicines and other literature (not limited to medicines) in which the issue of transparency of R&D costs was discussed. We took an international approach, focusing on high-income countries. The review revealed a large literature of relevance, with more than 13,000 'hits' to screen. After extracting and analysing data from 57 papers, including two recent reviews of empirical studies estimating the R&D costs of medicines, Rennane et al. 2021[4] and Schlander et al. 2021[5], the research team identified the following main findings from the literature.

Most empirical papers we found focused on R&D costs at the company or industry level and presented estimates of average R&D costs per medicine across samples of medicines. But two documents, both authored by non-governmental organisations (NGOs), presented the R&D costs of specific individual medicines. Papers generally refer to R&D costs up to the date of market authorisation. Further evaluations of the effectiveness of the new medicine may continue after this date, but the costs of that work are generally not included

in empirical estimates of R&D cost per new medicine.

Information on OOP costs, cost of capital and attrition rate differs between papers, ranging from primary sources, such as databases of company OOP costs and stock market data, to authors referencing other studies that calculate specific costs. The attrition rate – the proportion of candidates that enter the R&D process at various stages but do not receive market authorisation – can be calculated from published data, such as registers of clinical trials, but the papers' authors commonly reference attrition rates calculated in other published studies.

The papers found in the literature review cover a range of definitions of 'medicines' for which they present estimated R&D costs. Definitions range from an overall perspective of 'any new medicine'[6] or new molecular entities (NMEs) (a common approach), to very specific definitions, such as 'monoclonal antibodies'. R&D costs of adding new indications to existing medicines or producing combination medicines from existing medicines are not discussed in the papers we found.

Transparency was generally not defined explicitly. Implicitly, discussions of transparency concern the extent to which companies and other organisations that are conducting medicines R&D should publish data on their OOP R&D costs medicine by medicine. Some papers focused particularly on proposing that companies should publish data about the extent of public funding of the R&D of individual medicines, including via joint funding arrangements and tax credits.

Papers discuss transparency from the perspective of a few major stakeholder groups: industry, investors, healthcare payers, NGOs, regulators and policymakers. The payer perspective was the most frequently presented, with many papers proposing ways in which transparency about R&D costs could be improved. Most of the other papers were focused on R&D cost estimates and did not discuss transparency.

Information that should be made (more) transparent according to the reviewed literature includes: direct R&D costs incurred year by year, such as supplies and staff costs; indirect costs, such as overhead expenses; R&D timelines needed to bring new drugs to market; the cost of capital for medicines R&D; the costs of abandoned projects; and information about attrition rates and public contributions to drug R&D, such as indirect subsidies, incentives, tax credits and post-approval support.

We found some discussion of who is considered responsible for making R&D cost information more transparent, namely: pharmaceutical companies; the research community, which is called upon to improve on existing ways of calculating and publishing R&D costs; governments and their agencies, which, it is proposed, should analyse direct and indirect public funding for specific medicines; and the World Health Organization (WHO), who, it is proposed, can guide and support states to achieve R&D cost transparency.

A common argument in the literature reviewed was that pharmaceutical companies should make more detailed data available to the public. Some papers suggest that transparency can be enhanced by legislation and regulation to improve financial disclosure mechanisms and systems, similar to existing legislation and regulation requiring pharmaceutical companies to disclose payments to healthcare professionals and healthcare organisations. Others argue that transparency can be achieved by improving the quality of information systems, including financial reporting and media channels, as well as better-informed financial analysts and institutional investors.

Finally, when describing the impact that greater transparency around R&D costs of medicines might have, authors referred to expected advantages more frequently than to expected disadvantages. Expected advantages of greater transparency that are suggested in the literature include that it could lead to: improved decision making for investors; greater accountability of, and hence trust in, pharmaceutical companies; fairer medicines prices for payers; greater efficiency and better resource allocation by drug developers; a decreased burden for regulators; and more collaboration and verification opportunities for researchers. A potential disadvantage of transparency stated by more than one paper was the possibility of predatory use of R&D cost information by rival companies, which is argued to have the potential to discourage dynamic competition and so, ultimately, reduce access to new medicines. Three papers we found discuss the increased administrative burden associated with additional reporting to achieve greater transparency of R&D costs, but they give no indication of the magnitude of the additional cost.

Thus, what the implications would be, were greater transparency of R&D costs of individual medicines to be achieved, is currently unclear. Assertions are made that advantages would include 'fairer' prices, better investor decisions, better accountability and governance, and hence greater trust. Assertions are also made that greater transparency might feed predatory behaviour by commercial rivals to research-based pharmaceutical companies and would lead to additional administrative costs, both of which might damage the flow of new medicines. But evidence about the likely impact of greater transparency on medicines prices and how that can be expected to affect different countries, and evidence about the effect of that greater transparency on access to existing medicines and on future medicines innovation, is lacking.

Table of contents

Abbreviations and acronyms

CMA	(UK) Competition and Markets Authority
DNDI	Drugs for Neglected Diseases Initiative
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EEA	European Economic Area
EU	European Union
FDA	(US) Food and Drug Administration
IAVI	International AIDS Vaccine Initiative
LMICs	low- and middle-income countries
mAbs	monoclonal antibodies
MHRA	(UK) Medicines and Healthcare products Regulatory Agency
MMV	Medicines for Malaria Venture
NBE	new biological entity
NCE	new chemical entity
NGO	non-governmental organisation
NICE	(England) National Institute for Health and Care Excellence
NME	new molecular entity
OECD	Organisation for Economic Cooperation and Development
ONS	(UK) Office for National Statistics
OOP	out-of-pocket (expenditures)
PPP	public–private partnership
R&D	research and development
SEC	(US) Securities and Exchange Commission
TB	tuberculosis
WHA	World Health Assembly
WHO	World Health Organization

Chapter 1. **Background and context**

New medicines and vaccines are vital to healthcare but can have high prices attached. New medicines and vaccines (for brevity referred to collectively as 'medicines' in the present report from here on) depend on costly investments in research and development (R&D), and pharmaceutical companies seek to cover those costs via the prices they charge. But there is controversy around just how costly is the R&D entailed in bringing a new medicine to market. Calls for greater transparency about those costs are heard from policymakers internationally, most notably: by implication, in the 2019 World Health Assembly's (WHA) resolution WHA72.8 on 'Improving the transparency of markets for medicines, vaccines, and other health products' [1]; explicitly, in the European Commission's (EC) 2020 'Pharmaceutical strategy for Europe'[2], in which it commits to 'Engage with Member States in implementing non-legislative measures to improve transparency, such as guidelines on principles and costing methods for establishing the R&D costs of medicines'; and, also explicitly, in the US Congress' Inflation Reduction Act of 2022[3], which requires Medicare to negotiate prices for some medicines and for manufacturers to provide, as part of that negotiation, their R&D costs for the medicine in question[3].

This report presents a literature review undertaken in the autumn of 2022, aimed at determining what the literature says about the answers to the questions:

- How far and by what methods is it possible to identify the R&D costs of a new medicine and hence be transparent about them?
- What would be the implications, were greater transparency of R&D costs of individual medicines to be achieved, including implications for medicine pricing and innovation?

In the rest of this chapter, we set out the background and context for considering medicines R&D cost transparency. Chapter 2 describes how we conducted the review of both the academic and the non-academic ('grey') literature. We present the findings from the literature review in Chapter 3 and discuss them further in the concluding chapter, Chapter 4.

1.1. Medicines R&D and its costs

There is no dispute that the costs of researching and developing new medicines are substantial and the R&D process usually takes many years, with much uncertainty about the likelihood of any new medicine in the R&D pipeline eventually being authorised for use [7]. The public and charitable sectors have a major role in the early, basic science, stages of research. But as the R&D process progresses through discovery and preclinical stages to clinical trials (Phase I, Phase II and Phase III) and on to the research required to meet the regulatory environment criteria and standards, the role of the commercial sector becomes much greater. The focus of policy maker attention, and *de facto* of academic studies of R&D costs of medicines, has been on the costs of R&D conducted by commercial organisations. For that pragmatic reason, the focus of the present report is also on commercial organisations' R&D costs, although public and charitable sector costs

are mentioned where covered in the literature found.

There is much controversy over exactly how large the R&D costs of a new medicine are. A 2021 literature review by Schlander and colleagues[5] found that R&D costs range from $0.16–$4.54 billion per new medicine (in 2019 US dollars); some of the estimates included medicines developed by public–private partnerships (PPPs), but most were for commercially developed medicines. A similar review in 2021 by Rennane and colleagues[4] quotes a range of R&D costs from $0.11–$6.17 billion per new medicine (in 2018 US dollars). All of these estimates – and unless stated otherwise all other cost estimates presented in this report – refer to the pre-tax R&D costs incurred by commercial organisations. The reasons for the wide differences in estimates of R&D costs per medicine as revealed by these reviews are multifaceted. They include the sample of medicines included in the analysis, the period of study, the availability of data, and the methodology used to estimate the cost – for example how to allocate the costs of preclinical R&D when the same activity supports the R&D of multiple potential medicines, not just one.

When considering the R&D costs of a new medicine, what is meant by a 'new medicine' needs to be defined. At its most straightforward, a new medicine is a new molecular entity (NME) not previously authorised for use as a medicine[7]. However, it is the case that a medicine that is initially launched to treat patients with one indication may subsequently have its authorised therapeutic purpose extended to other indications. Researching and developing additional indications will usually entail additional studies, although they will not go through the full, traditional clinical development stages. Medicines may also be combined with other, already authorised molecular entities, and such novel combinations will also entail R&D costs. The definition of what is a medicine clearly has a direct effect on its R&D cost. The empirical studies found in the literature and discussed later in this report refer to the R&D costs of NMEs, but in so doing they put to one side other R&D costs associated with additional indications, repurposing existing medicines and producing combination products. Papers generally refer to R&D costs up to the date of market authorisation for a new medicine. Further evaluations of the effectiveness of the new medicine may continue after this date, but the costs of that work are generally not included in empirical estimates of R&D cost per new medicine.

The preceding paragraph provides examples of how the R&D process is often not a linear one of discovering a medicine, researching and developing it and then selling it. There is much non-linearity in the process, as is explained in detail by Hanney et al.[8]. Hence determining when to 'start the clock' and 'stop the clock' in order to attribute only costs incurred between those dates to the R&D of a specific medicine is not straightforward. The clock start is, de facto, when an organisation starts to make recorded R&D expenditures related to medicines, even if not to a specifically identified candidate medicine. The clock stop is commonly taken to be the date when marketing authorisation is given by a medicines regulator. But this date is not clear cut in some cases, due to increasing numbers of 'conditional' authorisations that are contingent on the medicine producer collecting more data before 'normal' authorisation will be given (or not). Furthermore, there are many medicines regulators, and the process for global approval can take years; hence the R&D costs incurred up to the date of first market authorisation is less than the eventual global total of R&D costs once the costs of submissions to all regulators have been included.

It is also the case that companies sometimes work jointly on the same project. Companies may merge with, or acquire, others along with their R&D pipelines, or they may acquire licensing rights to individual products in development. This market for technology means that some medicines are not researched and developed within a single company. Consequently, knowing the R&D costs of such medicines entails in these cases tracking the path of individual medicines as they pass from company to company as they proceed through the R&D process. The R&D cost of a new (successful) medicine, however defined, can be thought of as comprising three main elements[7], which we consider in turn in the following paragraphs:

1. 'Out-of-pocket (OOP) costs' of R&D incurred year by year
2. The cost of capital combined with the number of years it takes to bring a new medicine from discovery to being sold on the market for use with patients
3. The 'attrition rate', i.e. the percentage of successful medicines relative to the number researched at the outset.

1.1.1. Out-of-pocket costs

The total operating expenditures that an organisation incurs each year conducting R&D activities – commonly referred to in the literature as OOP costs – are reported in the published annual accounts of companies and other organisations. Such reporting is almost always at the aggregate, organisation-wide level, and does not present costs disaggregated per medicine. Where, as is often the case, different R&D activities are conducted in different countries (jurisdictions) and/or by different affiliates of the same parent company, the relevant R&D cost information must be sought in the consolidated accounts of that parent (or aggregated from the accounts published by the individual affiliates).

Accounting standards provide a degree of comparability between costs as recorded in different countries. However, what constitutes an R&D cost, rather than, say, a marketing cost or a manufacturing cost, may not be always clear cut. Such boundaries have in the past been a source of contention in the UK, for example, between pharmaceutical companies and the government department regulating the profits, and hence prices, of medicines sold to the National Health Service[9].

Some OOP R&D costs, for example those of a particular clinical trial or of preparing a dossier for seeking regulatory approval of a particular medicine, can readily be attributed to the medicine that is the subject of that trial or dossier, although that is not required in public reporting of company accounts currently. However, some other OOP costs, even if clearly part of R&D, are not incurred for a single medicine. For example, discovery costs (e.g. identifying and validating targets for research and then screening them) are generally not linked to a specific end product medicine, the identity or identities of which will only emerge over time, if at all.

In summary, while the notion of the OOP costs of R&D for a medicine, and hence of recording such costs in published accounts, may appear straightforward, it requires, in practice, a determination of: what is meant by a medicine; what is R&D as opposed to, say, marketing or manufacture; and how to allocate joint and non-product-specific costs across multiple medicines.

1.1.2. Cost of capital

The costs of R&D are incurred over a period of many years before a successfully developed medicine is authorised for use with patients. Consequently, the cost of capital is a major factor. The resources that are committed by investors to R&D in the hope of having a medicine to sell some years in the future are

resources that cannot then be put to some other use (the 'opportunity cost' in economic terminology), and investors will not earn their reward for many years even if the medicine is successful, i.e. it is launched on the market and purchased by healthcare payers. Some studies suggest that as much as half of the total cost of a new medicine may be due to the cost of capital[5]. There has been debate about the most appropriate approach to estimating the cost of capital, but there is no complete consensus[7, 10]. Pharmaceutical R&D is a highly risky activity, which means that the cost of capital is high and that much R&D expenditure is, in practice, funded by the internal resources (retained profits) of the company concerned, with a relatively small amount of debt financing. But some, typically newer and smaller, biopharmaceutical companies are more heavily dependent on debt or new equity. The cost of capital for an individual company is likely to depend on the characteristics of the company as well as on the risks associated with the particular medicines it is researching and developing.

As will be discussed further below, a commonly used approach to determining the cost of capital associated with R&D of medicines (plural) is to determine the weighted average cost of capital of companies investing in medicines R&D, drawing on stock market data and other capital market data. This approach provides empirical estimates of the cost of capital that take account of the riskiness of pharmaceutical R&D as an investment. But with the rare exception of a company researching and developing a single medicine and raising capital for no other purpose, this cost of capital will not be specifically that of an individual medicine. Rather, it will be an average cost of capital, i.e. a proxy for broadly similar investments, with similar levels of risk.

1.1.3. Attrition rate

To determine the R&D cost of a medicine that eventually proves successful, it is necessary to allow for the costs that were incurred in good faith pursuing candidates that eventually proved unlikely to be sufficiently effective or that were demonstrated in clinical trials not to be sufficiently effective to obtain authorisation for launch on the market[7, 11]. For every medicine launched, a higher number of medicines were put through Phase III clinical trials, an even higher number went into Phase II trials, a yet higher number had to enter Phase I trials, and many more were investigated but never got as far as being in a Phase I clinical trial[2]. The costs of failed R&D need to be allocated to the medicines that succeed. By definition, this attrition rate cannot be measured by recording the R&D cost history of a specific medicine that does make it to market. Information to enable estimation of approximate attrition rates between a medicine entering Phase I trials and reaching the market is readily available, recorded in publicly available sources, including clinical trials databases, such as https://clinicaltrials.gov/.

1.2. Policy relevance of a new medicine's R&D costs

At the beginning of Chapter 1 we referred to the high-level, international policy maker interest in making the R&D costs of new medicines more transparent. The policy challenge is to balance the interests of three groups: the patients who use medicines; the payers for healthcare (governments in tax-funded healthcare systems, social and private health insurers, and individuals who in some healthcare systems have to pay for medicines out of their own pocket); and the pharmaceutical industry and other organisations (including public and charity-funded R&D teams) that innovate

to research and develop new medicines. This policy context is also affected by the involvement in medicines R&D of the public and charitable sectors in combination with the commercial sector. Much basic and early-stage research, and a rather smaller proportion of clinical trials, are undertaken by the public and/or charity sectors. The large majority of later stages of R&D is carried out by the for-profit pharmaceutical industry.

The size of the R&D cost of a medicine, and specifically how much of that cost has been incurred by the commercial sector rather than public and charity-funded organisations, is important and controversial to the extent that it affects how much payers will pay for a new medicine, i.e. the medicine's price. But the price paid for new medicines is not just a cost to payers, it is also a vital signal to the pharmaceutical industry whether, and how much, to invest in researching and developing new medicines in future. If the price for a new medicine today is seen by investors as too low, they will not invest in the R&D that produces further new medicines in future, and this would not serve the interests of patients.

To ensure that new medicines continue to be discovered, researched and developed, but not at excessive cost, the price paid for any new medicine has, broadly speaking, to satisfy two requirements:

1. It should not exceed the value of the benefits the medicine yields.
2. It should not allow excessive ('supernormal' in economics jargon) profits for the producers of the medicine, or wasteful inefficiency by them, at the expense of the payers.

There are numerous ways in which medicines pricing can be regulated so as to attempt to meet these requirements. In essence they come down to attempts either to link a medicine's price to the value the medicine generates (often referred to as 'value-based pricing' or 'outcome-based payment') or to the costs of the organisations that sell the medicines (Mestre-Ferrandiz 2006[12] describes the range of such approaches). All these approaches are in use somewhere in the world, at least for some medicines, and in various combinations. Where prices are to be value or outcome based, the R&D costs of medicines become irrelevant. The costs do not determine the value or outcomes. On the other hand, if prices were to be regulated on a cost-plus approach, i.e. the price of a medicine set by adding a mark-up to its production and R&D costs, then ascertaining such costs would be imperative to calculate the price. However, cost-plus pricing is seldom used across the globe. The WHO goes so far as to recommend against cost-plus as the primary means to regulate prices, citing the current lack of transparency and the lack of a framework agreed upon among stakeholders regarding the inputs for price determination as the two reasons[13].

As noted earlier, the 2019 WHA resolution WHA72.8, on 'Improving the transparency of markets for medicines, vaccines, and other health products'[1], implies transparency of R&D costs of medicines while not explicitly calling for it. The WHA resolution in its final form includes provisions for countries to support transparency, but it does not advocate for publishing information on R&D costs for each medicine. This is despite earlier drafts of the WHA resolution requiring pharmaceutical companies to submit such internal information as a condition of registration and for governments to publish this[14]. We do not know the reasons for the lack of agreement on this issue, but they may well include that transparency of R&D costs (per medicine) is a complex issue, requiring further analyses.

The policy discussion around R&D costs transparency received more attention at the global policy level after the 2019 WHA resolution, when it was agreed by most countries to start publicly sharing information on the net prices they pay for medicines in their health systems. 'Net prices' are the amount received by manufacturers after subtraction of all rebates, discounts and other incentives. Similar provisions on medicines price transparency were included in a subsequent resolution, in September 2019, on universal health coverage endorsed by world leaders on the margins of the United Nations General Assembly[15]. The focus was on medicine prices, which are not the subject of our research (we are specifically concerned with transparency of R&D costs rather than of prices), but these resolutions were at least partly due to concerns about the role played by R&D costs as a driver of those prices.

The EC in its 2020 Pharmaceutical Strategy has expressed a desire for greater transparency of the R&D costs of medicines within the EU[2]. This was identified as a specific area of action where the EC would engage with EU member states, although limited to non-legislative measures such as guidelines on principles and costing methods for establishing the R&D costs of medicines.

In 2022 the US Inflation Reduction Act established a requirement for Medicare, the public health programme covering elderly and disabled Americans, to negotiate prices for some medicines and for manufacturers to provide as part of that negotiation their R&D costs for the medicine in question[3]. At the time of this writing, the US Government is in the initial phases of implementing these new requirements.

Thus, in summary, payers and policymakers concerned about the affordability of new medicines want to know more about what the costs of pharmaceutical company R&D of a new medicine are, by making those costs visible to external inspection and audit – in other words, by making them more transparent.

1.3. Extent of R&D cost transparency to date

Since 1979 there have been a number of empirical studies presenting estimates of the average R&D cost of a new medicine for various sample groups of medicines, both in the peer-reviewed academic literature and in the non-peer-reviewed, so-called 'grey' literature[5, 16]. The interest in publishing these one-off estimates is indicative of the absence of routinely published sources of the R&D costs of individual medicines.

Some information about medicines' R&D OOP costs is routinely available publicly in companies' (or other organisations') published, audited, annual reports and accounts. Given the multinational nature of the R&D work of many pharmaceutical companies, it may not be entirely straightforward to record all of these costs, but it is nevertheless done, in line with national accounting standards. However, this information is usually presented at the level of an organisation's total annual expenditure on R&D. Costs are not currently reported by medicine, other than in exceptional cases where a company has only one medicine in its R&D pipeline, in which case the company's total R&D costs in a year are the R&D costs of that medicine in that year. Some of the empirical estimates in the literature are based on such 'single-shot' companies' costs.

As already discussed in section 1.1.1, not all R&D costs are directly attributable to a single medicine. The, consequently arbitrary, allocation rules used to attribute preclinical costs to individual medicines represent an important factor in the studies estimating R&D costs per medicine. To avoid the need to

allocate such costs, discovery and preclinical phases are deliberately not included in some of the empirical estimations published in one-off studies[5].

Some medicines are subject to research and development by more than one company (or other organisation) as they progress through the R&D process. Currently there are no routine, published attempts to track R&D costs for the same medicine across different companies.

In addition to routine published sources of R&D cost data, some estimates in the empirical literature of R&D cost per medicine are based on one-off surveys of limited numbers of companies[17]. The raw data revealed by such surveys have not been published, however, although they may be available to contributing companies on an anonymised basis as part of benchmarking clubs (for one current example of this, see: https://clarivate.com/innovation-exchange/solution/cmr-international-pharmaceutical-rd-factbook/).

Data from the stock markets where pharmaceutical companies' shares are traded can be used to estimate the cost of capital faced by a company or group of companies in a given time period. But this cost of equity capital is unavoidably company or industry specific rather than medicine specific: the equity is in the whole company, not the individual medicine (unless the company is a 'single-shot' developer of a single medicine). Furthermore, an important minority of capital for investment in medicines R&D is obtained from venture capitalists or in the form of debt, rather than via publicly quoted shares. Data on the – commercially sensitive – costs of such capital are not necessarily available from public sources. Thus, overall, there is some information from which average costs of capital for R&D-intensive companies can be obtained, but not on a medicine-by-medicine basis.

The proportion of medicines candidates that are considered at some point in the R&D process but do not ever make it to launching on the medicines market is large. This attrition rate is by definition not medicine specific and might be most relevant at sector, or possibly disease, level rather than at company level given the role of the underlying science in affecting the likelihood of success. Data on the number and identities of medicines entering Phase I clinical trials, and the date of entry, are publicly available from registers of clinical trials (see https://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/search/), and data on medicines authorised are provided by the regulatory authorities (such as the European Medicines Agency (EMA) https://ec.europa.eu/health/documents/community-register/html/reg_hum_act.htm?sort=a and the US Food and Drug Administration (FDA) https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). It is possible to calculate industry-, company- or disease-wide attrition rates using data from these sources.

In summary, academic (and other) empirical studies provide published estimates of the average R&D costs of groups of medicines, but not of individual medicines. These one-off studies obtain data about OOP costs from a variety of sources that are either publicly available, routine data; data from anonymised, behind-paywall commercial services; or data that are simply not published. Costs of capital and attrition rates are unavoidably calculated across multiple medicines from data published by stock markets, medicines regulators and others. The resulting estimates of average R&D cost per new medicine differ hugely: a range of $0.1–6.2 billion (in 2018 US dollars) was reported by Rennane et al. in their 2021 review of empirical estimates[4], and a similarly wide range, of $0.2–4.5 billion (2019 US dollars), was reported by Schlander et al. in their review,

also published in 2021[5]. These estimates, despite the large ranges of values, also imply that R&D cost per medicine is increasing over time[4, 5].

In the rest of this report we present the methods and results of a review of academic and grey literature concerning the sources of data used to calculate R&D costs per medicine and this literature's discussion of the rationale for, feasibility of and consequences of greater transparency of R&D cost data for individual medicines.

Chapter 2. **Methods**

2.1. Academic literature search

We started from the published literature reviews by Schlander et al.[5] and Rennane et al.[4] of empirical estimates of the R&D cost of a medicine. We did not repeat those reviews but instead brought them up to date to August 2022 by using the same search strategies. We also added to them by also looking for papers discussing R&D cost transparency even if they did not include empirical estimates. We adopted a systematic approach to the literature review, combining the approaches used by Morgan et al.[18], Schlander et al.[5] and Rennane et al.[4] and including only literature where the methods used to collect the information and to estimate the R&D costs (per medicine) are explicit. We also only reviewed literature in the English language and limited our search geographically to European Economic Area (EEA) and Organisation for Economic Cooperation and Development (OECD), i.e. high-income, countries.

Search strategy – We developed our search strategy to identify papers estimating R&D costs per medicine and the challenges around data on costs per single product, by first revisiting the search terms provided in Schlander et al. 2021:

> a combination of the concepts of 'drug research and development' and 'costs' or 'drug research and development' and 'expenditure'.

Appendix 1 provides further detail.

We used the same three search engines as Schlander et al. 2021: Embase (OvidSP), PubMed and Econlit (EBSCO), but added searches of Google Scholar and Web of Science. We included studies at this stage that met four separate criteria in the full academic text review:

- Studies that provided estimates of the R&D cost of a medicine from 1 January 2020 to August 2022. This updated the searches conducted by Schlander et al.[5] and Rennane et al.[4], which were published in 2021 and covered the literature up to March 2020.[1]
- Studies that identified literature on R&D cost transparency (not limited to medicines R&D). Period covered: January 2012 to August 2022.
- Studies that discussed the 72nd WHA resolution, on 'Improving the transparency of markets for medicines, vaccines, and other health products'[1]. Period covered: 1 January 2019 to August 2022 (the Assembly took place in May 2019).
- Publications written in English.

An information specialist from RAND Knowledge Services carried out a database search using the terms identified in Appendix 1. This identified a total of 13,447 hits (see Figure 2 in Chapter 3).

1 Schlander et al. 2021 included all articles reviewed by Morgan et al. up until January 2010 and then carried out their own search covering the period 1 January 2010 to 5 March 2020.

Screening – Two researchers (MC, ZMN) carried out screening and prioritisation of the identified hits according to the title and abstract identified in the search. This led to the ultimate selection of 57 sources for full-text review.

Data extraction – Information was extracted by two researchers (MC, ZMN) into two separate Excel spreadsheets. The first data extraction sheet was designed for detailing the methods and sources used to derive empirical estimates of R&D costs and the second, to capture discussions and evidence around the topic of transparency in R&D costs and the WHA resolution. A pilot of the data extraction process was carried out before full data extraction commenced. Two researchers (MC, ZMN) carried out the pilot data extraction using one paper on the empirical estimates of R&D cost and one on R&D cost transparency. The full research team then discussed and made changes to the spreadsheet.

Snowballing – The final stage in the academic literature search was to carry out snowballing of references in the identified papers, that is, following up additional literature, both academic and grey, referenced by the authors of those papers so as to ensure review of all potentially relevant articles.

2.2. Grey literature search

The grey literature searching was carried out by one researcher with considerable knowledge of the subject area (JMF) and took place alongside the academic literature search, with frequent communication among the researchers involved in both searches. The basis for the grey literature search was google.com.

Search strategy and terms – The strategy for the search terms was based on the approach set out in the academic literature search. The Google search was aimed at finding sources on both empirical estimates of the R&D costs of medicines and discussions/evidence about transparency of R&D costs. The following search terms were used:

1. 'R&D costs medicines'
2. 'R&D costs medicines transparency'
3. 'research and development costs medicines transparency'
4. 'World Health Assembly resolution medicines'

Following the initial Google search, the same researcher then added searches in the websites of individual organisations identified from the research team's pre-existing knowledge of the subject area. These organisations are detailed in Table 1.

Table 1 – Grey literature search sources

Searching	Source	Dates of literature covered
Online searching	• Google	January 2010 to August 2022
Policy documents	• Health technology assessment bodies • National guidelines (EMA, FDA, MHRA, NICE) • Competition authority investigations (CMA, EC, US anti-trust) • OECD reports • EC reports • FDA reports	January 2010 to August 2022
Data sources	• Databases not behind a paywall • Public–private partnership websites (such as the International AIDS Vaccine Initiative (IAVI), the Medicines for Malaria Venture (MMV), the Global Alliance for Tuberculosis Drug Development (TB Alliance) and the Drugs for Neglected Diseases Initiative (DNDI)) • Office for National Statistics (ONS) Business Enterprise Research and Development Survey • The 2020 EU Industrial R&D Investment Scoreboard	January 2010 to August 2022

This identified a total of 78 sources (see Figure 1 in Chapter 3).

Screening – JMF carried out the screening and prioritisation of the hits according to the title and abstract identified in the screening and omitted any papers that are not relevant to the scope of our study or which had already been found in the academic literature review.

Data extraction – JMF extracted information using the same two separate Excel spreadsheets as were used for the academic literature data extraction. Another member of the team (JS) reviewed the information.

Snowballing – Snowballing of the identified literature was then carried out in the same way as for the academic literature to identify any additional relevant papers.

2.3. Literature synthesis

The literature synthesis was guided by the two main study questions:

- How far is it possible to identify, and hence be transparent about, the R&D costs of a new medicine?
- What would the implications be, were greater transparency of R&D costs to be achieved?

The focus for our literature synthesis was on identifying what the sources are presenting in terms of R&D cost transparency, where they

get the data from and to what extent the data are disaggregated. We considered what the literature reveals about the extent to which cost transparency already exists and what would be required to achieve greater transparency. Following data extraction of both the academic and grey literature, we conducted an internal workshop to identify key themes arising from the data extraction process.

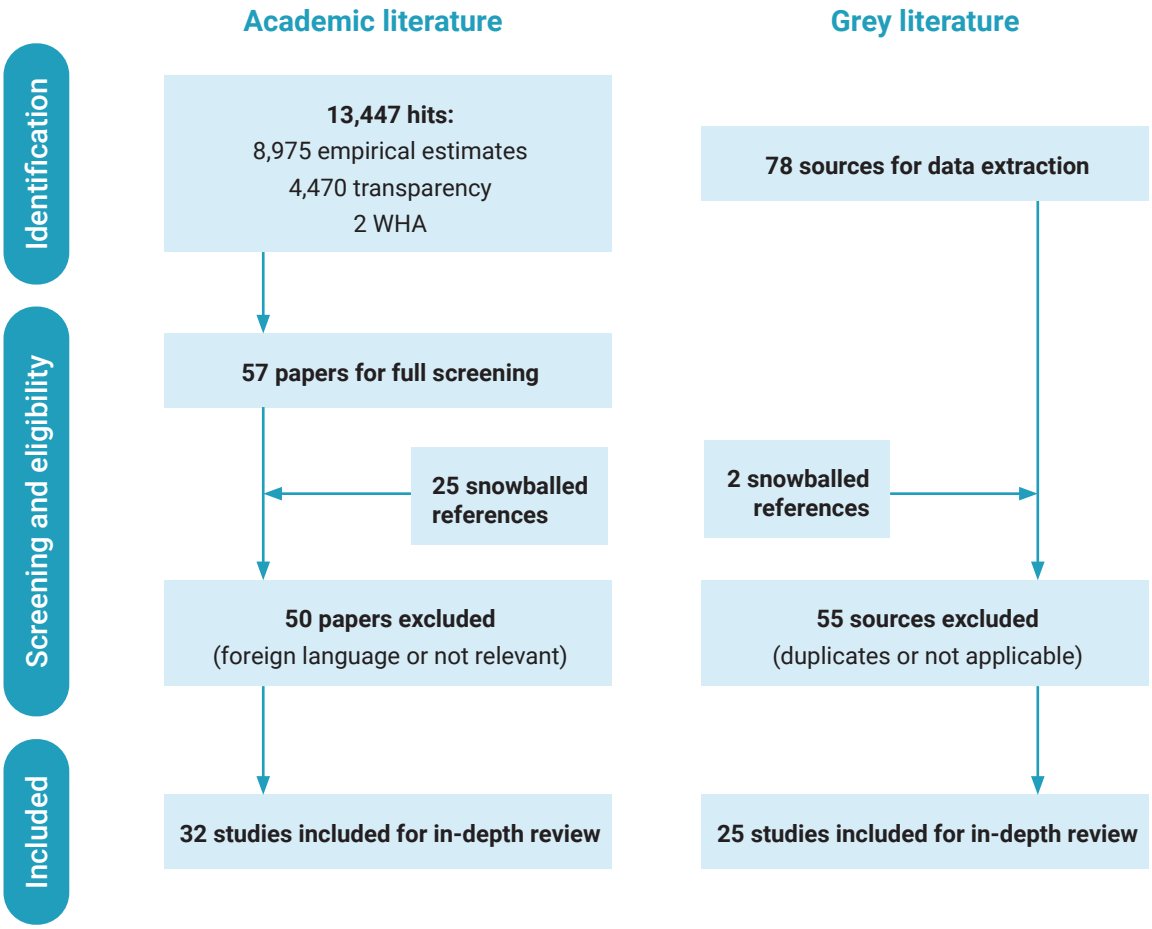
Chapter 3. **Findings**

This chapter reports the findings from the academic and grey literature search on R&D cost transparency. We first describe the number of sources identified for the review in terms of the overall number of 'hits' and then the final number used for data extraction following the screening process. We then go onto report the more detailed findings of the search, broken down into key headings and subheadings derived from the data extraction and literature analysis process. Subsections 3.2–3.5 cover issues around how R&D costs are defined, with what degree of disaggregation, and using what ultimate sources of data, as well as the particular definitions of a 'medicine' that are used in practice. Thus, these subsections address the first of the research questions, namely: How far and by what methods is it possible to identify the R&D costs of a new medicine and hence be transparent about them? Subsections 3.6–3.9 summarise what the literature we found says about how transparency appears to be defined from the perspectives of different interested groups, what actions are proposed to achieve greater transparency, and what are the expected advantages and disadvantages, were greater transparency to be achieved. Thus, these subsections address the second of the research questions, namely: What would be the implications were greater transparency of R&D costs of individual medicines to be achieved, including implications for medicine pricing and innovation?

3.1. Literature search results

The initial search process identified a large number of 'hits' (n=13,525). After initial screening of titles and abstracts, snowballing of references and final screening, this number was reduced to a total of 57 papers for full data extraction (32 academic papers and 25 items of grey literature). Appendix 2 provides full details of all 57 papers included in the review, and Figure 1 summarises the sifting process through the different phases of the review process.

Figure 1 – Academic and grey literature search and snowballing results



3.2. Type of R&D cost reported

The extent of medicine R&D costs covered in each paper we found in the empirical literature varies. Some studies estimate the total R&D costs of new medicines, namely OOP expenses incurred at all stages of the R&D process, together with the cost of capital and allowing for the attrition rate[4, 5, 19-24]. When all of these elements are taken into account, the result can be referred to as the total capitalised R&D cost of a successful new medicine. But other studies report R&D costs with varying levels of completeness. Some of these focus on the total OOP expenses but omit the cost of capital and the attrition rate[23, 25-28]. Some other papers include total OOP expenses plus the cost of capital but do not include the attrition rate[29]. Others combine total OOP expenses with attrition rates but omit the cost of capital[15, 30].

The remaining empirical studies found in the literature review only present partial OOP expenses. Some studies focus solely on the costs of clinical trials[6, 31-33]. One of these studies describes the costs of clinical trials and the cost of capital[34], while another details the costs of clinical trials, the cost of capital

and the attrition rate[35]. Preclinical and clinical trial costs are also reported together with the cost of capital and attrition rate[36]. Yet another paper discusses only Phases II and III of clinical trials, along with the attrition rate[37].

3.3. Level of disaggregation of R&D cost data

Most empirical studies focus on R&D costs at the company or industry level, but two present the R&D costs of specific individual medicines[28, 30].

Many of the empirical studies present the estimated total R&D costs of samples of medicines across the pharmaceutical industry[4-6, 15, 20-22, 25, 26, 31, 32]. Other studies present the estimated industry total for different countries, such as Canada[33], China[34] and Germany[38]; while another study discusses the estimated total R&D costs across a sample of countries[39].

Other studies focus on the estimated industry total R&D costs for medicines in specific disease areas, such as Alzheimer's disease[35, 37]. Another paper discusses the total industry costs for orphan vs. non-orphan drugs, subdivided into oncology vs. non-oncology drugs[36].

Farid et al.[23] consider the development and manufacturing costs across the biopharmaceutical drug development cycle by creating a model for three different scenarios: worst, average and best-case scenarios of different clinical trial phase success rates. Another article explores the estimated total costs for top-selling drugs[27]. Hassan et al.[29] focus on the costs of developing allogeneic cell therapies, but their paper is unclear about the type of costs used for all three key models. Instead, it states for one of the three models that it is based on the industry total of clinical trial development times and failure rates[29].

Two of the documents we found present R&D costs for individual medicines. Both are from the grey literature, and both are authored by NGOs drawing on the R&D that they were funding. The DNDI report presents OOP costs for eight treatments in its portfolio[28], and the Global Alliance for TB Drug Development (hereinafter TB Alliance)[30] presents R&D cost estimates for a new chemical entity (NCE) to treat tuberculosis (TB). These examples imply that when the research and development of a medicine are controlled by a single entity whose activity is specifically to do that, then it can be feasible to publish R&D cost data at the level of an individual medicine.

3.4. Ultimate source of cost data

There are several different sources of information used for estimates of R&D cost data, although the most widely cited is DiMasi et al.[40-47]. Information on OOP costs, cost of capital and attrition rate differs between studies, ranging from primary sources, such as databases of company OOPs and stock market data, to referencing other studies that calculate specific costs. Appendix 3 provides details of the sources cited for OOP expenses, cost of capital and attrition rates, where reported in included studies. Appendix 3 includes all sources identified in the academic literature (n=21), grey literature search (n=5) and the total of 25 sources included in the two review papers, namely Rennane et al.[4] and Schlander et al.[5].

3.4.1. OOP expenses

Of the 50 studies reporting estimates, 17 cite DiMasi et al.[19, 23, 33, 36, 40-52] as a source for cash expenses data. This is by far the single most cited source and is sometimes referred to as the Tufts Center for the Study of Drug Development's database (or Tufts database for short). This database includes information on multinational pharmaceutical firms, including

both foreign and US-owned firms, who provided data through a confidential survey of their new drug R&D costs[41, 44].

Other sources cited by more than one empirical paper are the Compustat[2] database[26, 27, 53] and the Cutting Edge survey[3][6, 31]. There are also several studies which report that they consulted expert elicitation for cash expenditure estimates[50, 54-56]. Several other studies[26, 36, 40-47, 57] report estimating their own total costs for cash expenses based on calculations using databases, such as Evaluate Pharma[21], or reported in other literature[24]. Two documents authored by NGOs present cost data from their own projects[28, 30]. In one study, the source for the OOP costs is not clear[29].

Whether the OOP R&D costs reported in empirical studies are total or partial, for example just covering one or more of the clinical trial phases, also varies. Many studies report their OOP cost estimates as being 'total' [4, 5, 19, 26, 27, 29, 36, 57, 58] or 'partial' expenses [4-6, 23-25, 30, 34, 36, 37, 59].

Those that provide total estimates reference databases, such as BioMed Tracker[20, 36] Compustat[8, 26] and 'Wind' macroeconomic database for China[4][57], as sources. Mestre-Ferrandiz and colleagues[7]used anonymised data provided by a company, CMR International, collected via a confidential survey of 16 companies. The TB Alliance conducted its own survey of clinical research organisations to obtain OOP cost data for a medicine it was sponsoring [30]. The table in Appendix 3, below, sets out the R&D cost sources for all of the empirical studies in our review, plus those in the Rennane et al.[4] and Schlander et al.[5] reviews.

The DNDI document[28] includes total OOP R&D costs for some of the medicines DNDI has developed but only partial OOP costs for others. The most commonly reported source when only partial costs were reported is clinical trial data, which is derived either from survey data[31], or the literature[6, 19, 23, 25, 36], or Securities and Exchange Commission (SEC) filings[37, 60] or non–publicly available databases[32]. The WHO COVID-19 candidate vaccine landscape database and SEC filing were more highly cited for publicly available clinical trial costs specific to vaccine trials. Studies also reported using commercial databases requiring payment or subscription to obtain clinical trial costs, such as the IQVIA CostPro Mid-Level Tool[32].

3.4.2. Cost of capital

The most widely reported method for estimating the cost of capital is the Capital Asset Pricing Model (CAPM)[7] method, which is referred to many times[6, 7, 33, 36, 37, 44, 46, 48, 53, 58, 61]. The magnitude of the real cost of capital used is frequently taken from DiMasi and colleagues[40-47], which is the single most frequently cited source, or from Scott et al.[56], who in turn cite DiMasi et al.[40]. The other method cited is the Fama-French method (cited by Falconi et al.[54] and Chit et al.[33]).

Other sources cited in the literature for calculating the cost of capital from stock market data are the BioMed Tracker[20] and Compustat databases[39], as well as other, literature sources, such as Mestre-Ferrandiz et

2 Compustat is a market and corporate financial database published by Standard and Poor's. It is publicly available.

3 Cutting Edge Information is a market research company.

4 Chinese database on industry, reportedly only accessible in China.

al.[7] (cited by Berdud et al.[36]) and Wouters et al.[58] (cited by Wouters et al.[22]).

3.4.3. Attrition rate

Of the 50 studies, 20 do not report data on attrition rate, and those studies that do report this data most often cite DiMasi et al.[40-47], followed by Scott et al.[19, 35, 37] (who themselves cite papers by DiMasi and colleagues and a number of other sources from the literature[20, 49, 51, 58]).

Other studies estimated attrition rates from databases, such as BioMed Tracker,[5] Trialtrove,[6] Compustat and Pharmaprojects.[7]

3.5. Definition of 'medicine'

The studies included in the review covered a range of definitions of 'medicines' for which they present estimated R&D costs. Definitions ranged from an overall perspective of 'any new medicine'[6] or NMEs (a common approach) to very specific definitions, such as 'monoclonal antibodies', which are identical antibodies produced by cloning a white blood cell line[25]. Heterogeneity of definitions of medicines reported in studies can make comparisons of R&D costs across studies complex. Different medicines and therapeutic class are often associated with differences in project success rates and pipelines inputs. The most commonly cited medical category included in the studies is 'new molecular entities' (NMEs), referring to a biologically active ingredient that has not previously been given market authorisation, e.g. by the US FDA [4, 5, 20, 21, 24]. One study uses a similar definition, although divorced from links to FDA authorisation, by referring to the medicines of focus as biopharmaceuticals, which are defined as any drug products synthesised or derived from biological sources[23].

Other medicines cited in the literature include monoclonal antibodies (mAbs) and allogenic cell therapies, which are medicines that use stem cells to prevent or treat disease[23, 25, 29]. More specific types of medicines studied were: orphan medicines[36, 61], vaccines and retrovirals[31, 33], antibiotics[15, 31] and medicines for Alzheimer's disease[19, 35].

3.6. Definitions of and perspectives on transparency

Transparency is often not defined explicitly. Implicitly, discussions of transparency concern companies and other organisations conducting medicines R&D being required to publish data on their OOP R&D costs medicine by medicine. One explicit and broad definition describes transparency as 'the availability of firm-specific information to those outside publicly traded firms'[62]. This definition is also used in a study arguing that corporate transparency across the board correlates with industry-specific growth[63]. Some papers propose that companies should publish data about the extent of public funding of the R&D of individual medicines, including via joint funding arrangements and tax credits[64].

A common way of approaching transparency is through the lens of financial disclosure. Frequently originating from accounting literature, these sources discuss the role of individual firms' disclosure of R&D expenditures[4, 32, 33, 39, 57, 65], as well as financial disclosure systems more broadly[38]. Some authors use this understanding of

5 This is a subscriber database of data collected about the drug development pipeline.

6 This is a subscriber database on clinical trial strategy, design, and execution.

7 This is a subscriber database on drug development, supplied by Citeline.

transparency as a proxy for a country's 'informational environment' and its relationship to innovation activity[39]. One source discusses transparency as an internal practice that should be improved within a specific pharmaceutical company[66].

Transparency of R&D costs is also discussed in relation to the need for more open-source approaches to collecting, processing and making data publicly available[67], or in relation to concerns about the use of data 'shielded from external scrutiny'[5], such as the frequently cited data used by DiMasi et al.[44].

Papers discuss transparency from the perspective of a few major stakeholder groups: industry, investors, payers, NGOs and others. Studies presenting information from an industry perspective emphasise that innovation in medicines is complex, and highly dependent on internal processes, learning, R&D and capital invested – most of which are not patentable, which means that there is no incentive to share them publicly[68]. Another article focuses on how uncertainty about future economic policy decisions creates a higher-risk environment, which the pharmaceutical industry tries to counterbalance by a reluctance to disclose R&D expenses in accounting statements[65]. These examples suggest that the pharmaceutical industry sometimes perceives transparency as a potential business threat, with the underlying assumption that information considered strategic should remain internal. Industry perspectives in the grey literature highlight undesirable consequences that might be expected to result from increasing transparency around companies' R&D costs for individual medicines – see section 3.9, below[69].

While the industry perspective is presented as being sceptical of increased R&D cost transparency, investors tend to be presented as being favourable to the idea. Some authors define investors as all actors funding R&D investments, whether they are from the private sector, government agencies, NGOs or academia[4]. According to some authors, investors perceive transparency positively, as it reduces uncertainty and helps inform decisions about future investments[4, 33, 34].

Another stakeholder group presented as supportive of improved transparency is the academic and research community, which are argued to be interested in achieving access to richer and more replicable data about R&D costs[57, 67, 70].

The perspective of payers – governments, insurers, NGOs and individual patients who pay for medicines when they reach the market – is the main perspective adopted either explicitly or implicitly in the literature. Almost all of the papers we reviewed that discuss R&D cost transparency refer to that perspective. Most frequently this perspective is expressed in terms of the consequences of R&D costs for medicine prices and a desire to know more about those costs so as to enable 'fairer' prices to be negotiated with industry. Some papers openly presume that prices of new medicines currently are above fair levels that balance the needs of payers, patients and industry[22, 27, 71].

Regulators and policymakers are two other groups, overlapping with payers, whose perspectives are considered in the literature. These groups include regulators making decisions about the type of financial disclosure systems that should be put in place[38], as well as the wider existing regulatory environment in which firms operate[65]. As these authors argue, regulatory frameworks are closely linked to what companies do and to the strategies they employ to not disclose information they consider commercially sensitive[65]. The literature refers to the importance that policymakers fully understand and make informed decisions about what form transparency requirements should take in any given context[14].

3.7. Actions proposed for achieving greater transparency

Many of the papers we reviewed propose ways in which transparency about R&D costs could be improved. Most of the other papers are focused on R&D cost estimates and do not discuss transparency.

3.7.1. The type of information to be made more transparent

Information that should be made (more) transparent according to the reviewed literature includes:

- Direct R&D costs incurred year by year, such as costs of supplies and staff[4, 17]
- Indirect costs, such as overhead expenses[4]
- R&D timelines needed to bring new drugs to market[4]
- The cost of capital for medicines R&D[4]
- Costs of abandoned projects and information about failures[4, 70]
- Public contributions to the drug development process, such as indirect subsidies, incentives, tax credits and post-approval support[71]
- Information on costs of patient engagement and participation in clinical trials, to allow an understanding of whether current practices are cost-effective and feasible[32]
- The total societal costs of drug development, beyond prices and direct research funding[71].

Schlander et al.[5] discuss how the lack of transparency in published estimates of average R&D costs 'masks the essential sources of heterogeneity' (p1266), such as differences in therapeutic area (often associated with differences in project success rates), orphan vs non-orphan drugs, and firm size. They recommend that future studies include consideration of neglected variables and of the 'trade-off between the transparency and public accessibility of data and their specificity' (p1266).

3.7.2. Who is responsible for making R&D cost information more transparent

We have also identified discussion in some of the literature concerning who should be making the R&D cost information more transparent. This includes four major groups of stakeholders:

- Pharmaceutical companies[4, 22, 26, 32, 71]
- The research community, which is called upon to improve on existing ways of calculating and publishing R&D costs[17, 33, 67, 70]
- Governments and their agencies, which, it is proposed, should analyse direct and indirect public funding for specific medicines[71]
- The WHO, which, it is proposed, can guide and support states to achieve R&D cost transparency[72, 73].

3.7.3. Ways in which R&D costs of medicines could be made more transparent

The most common argument we found in the literature reviewed is that pharmaceutical companies should make more detailed data available to the public[4, 22, 26, 32, 71]. Some studies suggest that transparency can be enhanced by legislation and regulation to improve financial disclosure mechanisms and systems[38, 57, 62, 65, 72, 74-76], and some cite parallels with legislation and regulation requiring pharmaceutical companies to disclose payments to healthcare professionals and healthcare organisations[77]. Others

argue that transparency can be achieved by improving the quality of information systems, including financial reporting and media channels, and hence better informed financial analysts and institutional investors[62]. Another suggestion for how to enhance transparency of R&D costs involves improving the reporting of R&D costs within a pharmaceutical company by using a bespoke online financial reporting tool[66].

Improving public–private collaborations, where both public and private institutions invest and share in development risk, is also argued to have the potential to increase transparency of R&D costs because of the assumption that this would enable governments and public institutions to have direct access to R&D cost information[21].

Some authors focus on costs of R&D explicitly in the academic context. They argue that transparency can be improved by funding projects that utilise open-source data made available online[67], including all raw, virtual and laboratory data in publications, so that anyone with knowledge of the subject would be able to review, critique and verify it[67].

3.8. Expected advantages of greater transparency

A number of expected advantages of greater transparency around R&D costs of new medicines are mentioned by authors in the literature we reviewed. The suggested advantages include that it could lead to improved decision making for investors; greater accountability of, and hence trust in, pharmaceutical companies; fairer medicines prices for payers; greater efficiency and better resource allocation by drug developers; a decreased burden for regulators; and more collaboration and verification opportunities for researchers.

Several studies report that investors would be among the main beneficiaries of greater transparency, arguing that it would improve their decision making[4, 33, 34, 38, 63, 65]. Chit et al. suggest that if investors were to know more about the robustness of the estimates of costs for vaccines and drugs, this might reduce uncertainty in the debate about bias in the cost of R&D and also help better inform pricing[33]. Dinh et al. argue that greater transparency might benefit companies, finding that those with greater R&D disclosure generally have a lower cost of capital and higher market value[38]. This finding is also highlighted by Wang et al., who discuss a significant and positive association between capitalised R&D and market value[34]. In other words, greater transparency of R&D costs might lead to reduced Information asymmetries between companies and capital markets[39], potentially leading to more informative stock prices[63] and an environment within which investors can make better decisions[65].

A more or less explicit theme in many of the papers we reviewed is that greater transparency around the R&D costs of individual medicines is necessary for good governance and accountability, and that with such accountability trust – by payers, patients and investors – would be reinforced (see, for example, [69, 72, 78]).

Many papers argue that healthcare payers (i.e. governments, insurers, patients, national health services) would benefit from heightened transparency of R&D costs, with the assumption that more transparency leads to ‘fairer’ drug prices[71]. More specifically, some papers argue that transparent R&D costs within a company[66] or across the entire pharmaceutical industry[22] would incentivise and enable policies that, in the view of the authors, would better regulate medicine prices by reference to underlying costs. This, the authors expect, would result in lower

prices and hence more affordable medicines for patients[67, 71]. The assumption that transparency provides a clear pathway towards fairer-priced medicines is further reflected in the WHA resolution, which posits that transparency encourages more competition and lower prices of medicines[14].

A further argument for greater transparency in R&D costs identified in the literature is that it might lead to better resource allocation by drug developers[38, 39, 63, 71, 74]. R&D expenditure information is important not only in estimating a firm's future performance and therefore how it prioritises its budget and spending plans[38, 63, 71], but also in translating to positive liquidity and valuation[74], lower cost external and arm's length financing[39, 63].

Tax authorities and financial regulators and auditors are argued to potentially benefit from greater R&D cost transparency[26], by reducing problems that have been referred to as information frictions[63]. These authors argue that corporate transparency might facilitate investment efficiency and, at a macro level, contribute to more efficient allocation of scare resources. Transparency of R&D costs could also reveal the cost consequences of the medicines regulatory frameworks that, in effect, mandate some R&D expenditures[71], for example, by measuring whether regulation is too burdensome or costly[32]. Chen et al.[70] focus on China as an emerging market where intellectual property rights are less developed. They find a significant positive association between R&D expenditure disclosure and the number of patents a firm has, which, they argue, reinforces that R&D cost transparency benefits drug developers by incentivising improved allocation of resources and investment [57].

In the context of arguing for greater transparency in medicines discovery and development, Årdal and Røttingen[70] assert that a more 'open-source' approach should lead to a reduction in duplicative research and may lead to more collaboration. They suggest that such tools as publicly available registries, biobanks and open access publications are desirable[70]. A further two studies suggest that improved information and transparency could lead to better measurement of R&D productivity, allowing for more efficiency and improvements in practice[17, 39]. This could then benefit R&D of drugs for neglected diseases, where there is little market incentive, by facilitating reduced costs due to the improvements in efficiencies[67].

3.9. Expected disadvantages of greater transparency

Overall, potential disadvantages of greater R&D cost transparency are referred to in the literature less often than benefits. One potential disadvantage stated is the possibility of predatory use of R&D cost information by rival companies[14, 69]. The papers describe this as competitor firms being able to assess a disclosing company's commercial strategy and then use that information to act in predatory ways (also identified by Sengupta[68]). This is argued to have the potential to discourage dynamic competition and so, ultimately, reduce access to new medicines. Brown and Martinsson[39] highlight that the costs associated with information leakage to competitor firms are 'particularly severe when it comes to the development of new products and ideas' (p.1600), stating that 'if these proprietary costs are sufficiently large, then transparency can discourage innovative efforts' (p.1600).

Sengupta[68] and Shaw and Mestre-Ferrandiz[14] go on to argue that pharmaceutical companies may be deterred from offering discriminatory prices favourable to low- and middle-income countries if the companies' R&D costs for a medicine are more

transparent if that were to result in lower prices being negotiated in high-income countries. Shaw and Mestre-Ferrandiz[14] state that this is especially true if there is international reference pricing.

Finally, three papers[5, 51, 79] discuss the increased administrative burden associated with additional reporting to achieve greater transparency of R&D costs, but they give no indication of the magnitude of the additional cost.

Chapter 4. **Discussion and conclusions**

4.1. Discussion of findings

We set out to discover what the academic and grey literatures say about the answers to the questions:

- How far and by what methods is it possible to identify the R&D costs of a new medicine and hence be transparent about them?
- What would be the implications were greater transparency of R&D costs of individual medicines to be achieved, including implications for medicine pricing and innovation?

Starting from reviews of the empirical literature presenting estimates of the R&D cost of a new medicine by Rennane et al. 2021 and Schlander et al. 2021[4, 5], we searched for more recent papers of that kind and additionally searched for papers discussing R&D cost transparency or the WHA resolution advocating that[1]. The resulting literature was large, with over 13,000 hits in our initial targeted search, leading to 57 papers for data extraction, including the Rennane et al. 2021[4] and Schlander et al. 2021[5] literature reviews. Consideration of R&D cost transparency in the pharmaceutical industry is clearly topical.

4.1.1. How far and by what methods is it possible to identify the R&D costs of a new medicine and hence be transparent about them?

As described earlier in this report, the R&D cost of a medicine comprises the OOP costs incurred year by year by the organisations undertaking the R&D, plus the cost of capital (given that the expenditure to research and develop a particular medicine typically occurs over many years), plus an allocation of the costs of R&D that do not ultimately lead to a medicine with market authorisation (i.e. the attrition rate). The literature contains a steadily growing number of empirical estimates of some or all of the R&D costs of a medicine, over various time periods and for various groups of medicines. Each of these empirical estimates is essentially a one-off exercise, although some authors have provided updated estimates some years after their original studies (e.g. DiMasi et al. and Wouters et al.[22, 40-47, 58]).

There is currently no routine publication of data on the R&D costs of individual medicines. To achieve greater transparency, implying routine publication of that kind of data, has become the focus of a growing literature and of international policy pronouncements, notably by the WHA[1], the European Commission[2] and the US Federal Government[3].

The findings of our literature review indicate that a substantial minority of current estimates are based on one unpublished database of medicines R&D costs – the DiMasi/Tufts data – but that there are several other sources that have been used. Some are the open databases of public authorities, such as the US SEC, and others are available behind a paywall from commercial providers of data. Published estimates based on these various sources are nearly always for the average cost per medicine over samples of medicines of varying sizes and scopes, rather than for the R&D cost of a specific named medicine, and the magnitudes of the resulting cost estimates vary widely[4, 5]. Within this general picture,

however, it is notable that two NGOs have published their own one-off estimates of the total R&D costs of each of the named individual medicines in their respective pipelines[28, 30]. This indicates what is possible, at least for organisations focused on medicines R&D for a small number of medicines.

That all of the published R&D costs per medicine figures are estimates, based in part on assumptions, is unavoidable. To calculate the R&D cost of a specific medicine requires more than the collection of annually incurred OOP R&D cost data. Even to do that requires assumptions to be made about: how to allocate joint and non-product-specific costs to different individual products; the appropriate cost of capital to apply; and what is the appropriate attrition rate; so that the costs of all R&D are allowed for, including the R&D that has not (yet) resulted in a medicine receiving market authorisation. It is not yet possible to read anywhere the R&D expenditure that has been incurred on each of the many medicines that are in the R&D pipelines of companies and other organisations in any year. Data on the cost of capital are only calculable from routinely available data at the organisation level, and the cost of capital is commonly calculated on a whole-industry basis, or at least across all of those companies in the industry whose equity is traded on a particular stock market. The attrition rate can be calculated from clinical trial registers and the lists of medicines eventually receiving market authorisation, but by definition this rate is not specific to an individual medicine that succeeds in reaching the market.

Most of the literature we found on empirical studies and on discussion of transparency, including the empirical studies reviewed by Rennane et al.[4] and Schlander et al.[5], focuses on the R&D cost per NME. However, a non-negligible amount of R&D cost is, in practice, incurred when adding to the indications for which already-marketed NMEs may be authorised; to research and develop combination products; and to undertake post-launch research to reduce uncertainties about the effectiveness of already-marketed medicines. We found no discussion in the literature of how R&D cost transparency might be expected to allow for such expenditures, but appropriate transparency around them is an issue that would need to be resolved if increased transparency of the costs of NMEs were to be mandated at some future date.

4.1.2. What would be the implications were greater transparency of R&D costs of individual medicines to be achieved, including implications for medicine pricing and innovation?

We have not found an explicit definition of the meaning of 'R&D cost transparency', but it certainly includes the publication of more data than are currently published. Even though the definition of R&D cost transparency is vague, a number of reasons are given for seeking more of it. In explaining this desire, the most commonly expressed perspective in the medicines R&D cost transparency literature seems to be that of the payer. Government bodies, health insurers (whether social insurers or commercial) and NGOs are seeking more R&D cost information from the organisations undertaking that R&D, and this information is frequently stated as being essential to permit negotiation of 'fairer' prices for new medicines. The underlying assumption in these cases is, either explicitly or implicitly, that the prices of at least some new medicines are considered from this perspective to be too high. Linked to the point about 'fairer' prices is the argument around the need to ascertain the share of publicly funded R&D within the medicines R&D process.

But there are other motivations, too, for the calls for greater transparency around R&D costs of medicines. Potential future, as well

as current, investors could benefit by being able to make better future decisions from knowing more about the costs of the particular R&D process they are being asked to invest, or have already invested, in. Transparency is also seen as a building block for trust between payers and industry, as a requirement of public accountability and good governance, given the public's great interest in the outcomes of medical research both as patients and as the ultimate payers (via taxes, insurance premia and personal expenditures on medicines).

Possible disadvantages of increased R&D cost transparency are mentioned less frequently in the literature we reviewed. From an industry perspective, concerns have been expressed that publishing more cost information, including the extent of publicly funded support for R&D of medicines, may enable predatory behaviour by rival companies. There are also administrative costs to collecting, auditing and publishing more disaggregated R&D cost information. In principle, there could be a disadvantage were published R&D costs of individual medicines to be based on arbitrary allocations of joint or non-product-specific costs – a disadvantage in the sense that some information would be lost in an allocation process and it therefore might be more informative not to allocate across medicines those costs that are not incurred for a specific medicine alone. However, the literature we found does not go into this level of detail about how R&D cost transparency might be implemented in practice.

The literature offers, at a high level, proposals for achieving greater transparency about all of the elements that comprise the R&D cost of a medicine: the OOP expenses, the cost of capital and the attrition rate. Four major stakeholder groups were identified as having a role in achieving greater transparency: the pharmaceutical companies and other organisations that conduct the R&D and incur the costs; the research community more generally, including academia; governments and their agencies; and the WHO. Ways proposed to support greater transparency range from legal requirements on companies and other organisations to publish more detailed R&D cost data, to improving the quality of information systems, to a greater role for public–private partnerships where public bodies share the research and development work and hence the information about the costs of those activities. We suggest, based on our analysis of the literature, that a helpful way to advance consideration of greater R&D cost transparency might be to work up options for the details of how that might be done. This would permit more focus in the discussions among stakeholders. The findings from our literature review also imply that it would be desirable to learn more about the extent to which organisations – companies, NGOs, universities and other public or charity-funded laboratories – that carry out medicines R&D already collect cost data in a way that could form the basis of published costs. The greatest steps in this direction appear currently to have been taken by two NGOs: DNDI[28] and TB Alliance[30]. To what extent could their approach be replicated elsewhere or taken further?

With a clearer idea of what greater transparency of R&D costs would look like, the implications of that transparency remain to be worked through in detail. A major focus in the literature currently is on such information being an input to pricing and reimbursement negotiations between producers of new medicines and the organisations that pay for them or that act on behalf of payers. The specifics of pricing and reimbursement vary from country to country. Consequently, the impact that greater R&D cost transparency might have, either within current pricing and reimbursement arrangements or in stimulating

changes to those arrangements, is likely to vary between healthcare systems: what would happen to price levels, and would price negotiations be speeded up or slowed down? Hence the impact, if any, on future prices of medicines is not only currently unclear but also likely to vary from place to place. Given the uncertainty about how new medicines' prices might be affected, there is *a fortiori* uncertainty about the consequences for investment in researching and developing new medicines in future. Clearly, much uncertainty remains, and work is needed to start to gather evidence about the likely impact of increased R&D cost transparency to the extent it may be practicable.

4.2. Strengths and limitations of the literature review

Our literature review findings are inevitably limited by the way in which we searched for relevant papers. For the search of peer-reviewed, 'academic' literature, we were able to start from the strong foundations provided by two recently published, peer-reviewed reviews of empirical literature: we used the same search strategies as used by Rennane et al.[4] and by Schlander et al.[5] but updated them to the summer of 2022. We undertook a search for additional academic literature discussing R&D cost transparency in any sector, not limited to medicines, using a broad range of terms. The result was more than 13,000 hits, which we then thoroughly screened. The main limitation to this part of the literature review was that for pragmatic reasons we included only papers written in the English language. We would expect that there are likely to be further discussions of interest published in other languages. We also restricted our review to papers about EEA and OECD countries, where the large majority of R&D expenditure takes place and where the large majority of capital is raised to invest in medicines R&D.

For the subject of this study, medicines R&D cost transparency – which is a focus of active policy interest internationally – it was clear that much potentially important literature would be outside the peer-reviewed, 'academic' literature, that is, it would be found in the 'grey' literature. To search for such papers, we undertook a broad Google search and additionally searched on the websites of specific organisations that were, to the research team's knowledge, likely to have produced such papers. The Google search had, for pragmatic reasons in view of the very large number of hits found and the inevitable resource limits for our study, to be limited to those on the first three pages of 'hits' that were reviewed. Although members of the research team have been active in the area of medicines R&D policy for many years, it is also possible that we may have been unaware of and hence omitted specific organisations of relevance. The grey literature search was also limited to English-language papers and with relevance to high-income countries (EEA and OECD). Thus, the grey literature search was not comprehensive but, rather, aimed to be systematic and robust in approach while being efficient. The researchers are confident that it will have yielded the large majority of relevant arguments and evidence that have been published.

4.3. Summary and conclusions from the literature review

The literature review reported here has revealed many papers relevant to the topic of medicines R&D cost transparency. Empirical estimates are based on several ultimate sources of data on the OOP costs incurred by organisations researching and developing new medicines, although many papers are based on a handful of sources, most notably the confidential database used by DiMasi and colleagues. Published sources of data on the cost of

capital and on attrition rates are available, but these data require analysis to generate costs, and they inevitably do so for groups of medicines rather than individual medicines, except for the rare cases where an organisation has just one medicine in its R&D pipeline or for the case of specific NGOs involved in medicines R&D for neglected diseases.

The empirical and non-empirical literatures taken together indicate that it is possible to generate estimates of the R&D costs of individual medicines, but that these are unavoidably based on assumptions about how to allocate some costs. Those assumptions can themselves be made transparent, as they have been in one-off academic studies.

A range of actions are proposed in the literature to increase R&D cost transparency, including legislation, guidance and promulgation of improved information systems. Governments and their agencies, the WHO, and other organisations able to support and encourage transparency, and the companies and other organisations, as well as the researchers actually undertaking the R&D, are all seen as having roles.

The implications of greater transparency of R&D costs of individual medicines, were that to be achieved, are currently unclear. Assertions are made that benefits would include 'fairer' prices, better investor decisions, better accountability and governance, and hence greater trust. Assertions are also made that greater transparency might feed predatory behaviour by commercial rivals to research-based pharmaceutical companies and would lead to additional administrative costs, both of which might damage the flow of new medicines. But evidence about the likely impact of greater transparency on medicines prices and how that can be expected to affect different countries, and evidence about the effect on access to existing medicines and on future medicines innovation, is lacking.

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Appendix 1. **Search terms**

Database searched	Search sequence
1. Empirical estimates of R&D cost of a medicine	
Google Scholar	intitle:"pharmaceutical") AND (intitle:"cost" OR intitle:"economics" OR intitle:"expenditure" OR intitle:"spend") AND (intitle:"research" OR intitle:"development" OR intitle:"innovation" OR intitle:"investigation" OR intitle:"R&D") (intitle:"biopharmaceutical") AND (intitle:"cost" OR intitle:"economics" OR intitle:"expenditure" OR intitle:"spend") AND (intitle:"research" OR intitle:"development" OR intitle:"innovation" OR intitle:"investigation" OR intitle:"R&D") (intitle:"drug") AND (intitle:"cost" OR intitle:"economics" OR intitle:"expenditure" OR intitle:"spend") AND (intitle:"research" OR intitle:"development" OR intitle:"innovation" OR intitle:"investigation" OR intitle:"R&D") (intitle:"medicine") AND (intitle:"cost" OR intitle:"economics" OR intitle:"expenditure" OR intitle:"spend") AND (intitle:"research" OR intitle:"development" OR intitle:"innovation" OR intitle:"investigation" OR intitle:"R&D") (intitle:"vaccine") AND (intitle:"cost" OR intitle:"economics" OR intitle:"expenditure" OR intitle:"spend") AND (intitle:"research" OR intitle:"development" OR intitle:"innovation" OR intitle:"investigation" OR intitle:"R&D")
PubMed	(pharma*[Title/Abstract] OR biopharma*[Title/Abstract] OR drug[Title/Abstract] OR medicine[Title/Abstract] OR vaccine[Title/Abstract]) AND (cost[Title/Abstract] OR economic*[Title/Abstract] OR expenditure[Title/Abstract] OR spend*[Title/Abstract]) AND (research[Title/Abstract] OR development[Title/Abstract] OR innovation[Title/Abstract] OR investigation[Title/Abstract] OR "R&D"[Title/Abstract]) Exclude: publication types: Adaptive Clinical Trial OR Clinical Study OR Clinical Trial OR Clinical Trial, Phase I OR Clinical Trial, Phase II OR Clinical Trial, Phase III OR Clinical Trial, Phase IV OR Clinical Trial Protocol OR Clinical Trial, Veterinary OR Controlled Clinical Trial OR Randomized Controlled Trial OR Randomized Controlled Trial, Veterinary OR Pragmatic Clinical Trial OR Multicenter Study OR Editorial OR Published Erratum OR Letter OR Review
EconLit	(AB pharma* OR biopharma* OR drug OR medicine OR vaccine) AND (AB cost OR econom* OR expenditure OR spend*) AND (AB research OR development OR innovation OR investigation OR "R&D")

Database searched	Search sequence
Embase	(pharma* OR biopharma* OR drug OR medicine OR vaccine).kw,ti. AND (research OR development OR innovation OR investigation OR "R&D").kw,ti. AND (cost OR econom* OR expenditure OR spend*).ab,ti. Exclude ((clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or Phase 1 clinical trial or Phase 2 clinical trial or Phase 3 clinical trial or Phase 4 clinical trial) and (abstract report or "book review" or conference abstract or "conference review" or editorial or erratum or letter or note or patent or "review" or short survey or tombstone))
Web of Science	(pharma*[Title/Abstract] OR biopharma*[Title Abstract] OR drug[Title/Abstract] OR medicine[Title/Abstract] OR vaccine[Title/Abstract]) AND (cost[Title/Abstract] OR economic*[Title/Abstract] OR expenditure[Title/Abstract] OR spend*[Title/Abstract]) AND (development[Title/Abstract] OR "R&D"[Title/Abstract]) Exclude: Document types: Book Review OR Editorial Material OR Meeting Abstract OR Meeting Summary OR Proceedings Paper OR Review OR Letter OR Note OR Correction
2. R&D cost transparency	
Google scholar	Intitle: (cost OR economic OR expenditure OR spend OR spending) AND (research OR development OR "r&d") AND (transparency OR transparent OR disclosure OR disclosed OR disclosing OR disaggregated OR disaggregation OR granular OR granularity OR ambiguity OR ambiguous)
Pubmed	(cost[Title/Abstract] OR economic*[Title/Abstract] OR expenditure[Title/Abstract] OR spend*[Title/Abstract]) AND (research[Title/Abstract] OR development[Title/Abstract] OR "R&D"[Title/Abstract]) AND (transparen*[Title/Abstract] OR disclos*[Title/Abstract] OR disaggregat*[Title/Abstract] OR granular*[Title/Abstract] OR ambigu*[Title/Abstract]) Exclude: publication types: Adaptive Clinical Trial OR Clinical Study OR Clinical Trial OR Clinical Trial, Phase I OR Clinical Trial, Phase II OR Clinical Trial, Phase III OR Clinical Trial, Phase IV OR Clinical Trial Protocol OR Clinical Trial, Veterinary OR Controlled Clinical Trial OR Randomized Controlled Trial OR Randomized Controlled Trial, Veterinary OR Pragmatic Clinical Trial OR Multicenter Study OR Editorial OR Published Erratum OR Letter OR Review

Database searched	Search sequence
EconLit	(AB pharma* OR biopharma* OR drug OR medicine OR vaccine) AND (AB cost OR econom* OR expenditure OR spend*) AND (AB research OR development OR innovation OR investigation OR "R&D")
Embase	(research OR development OR "R&D").kw,ti. AND (cost OR econom* OR expenditure OR spend*).ab,ti. AND (transparen* OR disclos* OR disaggregat* OR granular* OR ambigu*).ab,ti. Exclude ((clinical trial or randomized controlled trial or controlled clinical trial or multicentre study or Phase 1 clinical trial or Phase 2 clinical trial or Phase 3 clinical trial or Phase 4 clinical trial) and (abstract report or "book review" or conference abstract or "conference review" or editorial or erratum or letter or note or patent or "review" or short survey or tombstone))
Web of Science	(cost[Title/Abstract] OR economic*[Title/Abstract] OR expenditure[Title/Abstract] OR spend*[Title/Abstract]) AND ("research and development"[Title/Abstract] OR "research & development"[Title/Abstract] OR "R&D"[Title/Abstract]) AND (transparen*[Title/Abstract] OR disclos*[Title/Abstract] OR disaggregat*[Title/Abstract] OR granular*[Title/Abstract] OR ambigu*[Title/Abstract]) Exclude: Document types: Book Review OR Editorial Material OR Meeting Abstract OR Meeting Summary OR Proceedings Paper OR Review OR Letter OR Note OR Correction
3. 72nd World Health Assembly	
Google Scholar	("World Health Assembly" OR "WHA") AND resolution AND (transparency OR transparent OR disclosed OR disclosing OR disclosure OR disaggregated OR disaggregation OR granular OR granularity OR ambiguity OR ambiguous)
Pubmed	("World Health Assembly"[Title/Abstract] OR WHA[Title/Abstract]) AND (resolution[Title/Abstract]) AND (transparen*[Title/Abstract] OR disclos*[Title/Abstract] OR disaggregat*[Title/Abstract] OR granular*[Title/Abstract] OR ambigu*[Title/Abstract]) Exclude: publication types: Adaptive Clinical Trial OR Clinical Study OR Clinical Trial OR Clinical Trial, Phase I OR Clinical Trial, Phase II OR Clinical Trial, Phase III OR Clinical Trial, Phase IV OR Clinical Trial Protocol OR Clinical Trial, Veterinary OR Controlled Clinical Trial OR Randomized Controlled Trial OR Randomized Controlled Trial, Veterinary OR Pragmatic Clinical Trial OR Multicenter Study OR Editorial OR Published Erratum OR Letter OR Review

Database searched	Search sequence
EconLit	(AB "World Health Assembly" OR WHA) AND (resolution) AND (transparen* OR disclos* OR disaggregat* OR granular* OR ambigu*)
Embase	("World Health Assembly" OR WHA).kw,ti. AND (resolution).kw,ti. AND (transparen* OR disclos* OR disaggregat* OR granular* OR ambigu*).ab,ti. Exclude ((clinical trial or randomised controlled trial or controlled clinical trial or multicentre study or Phase 1 clinical trial or Phase 2 clinical trial or Phase 3 clinical trial or Phase 4 clinical trial) and (abstract report or "book review" or conference abstract or "conference review" or editorial or erratum or letter or note or patent or "review" or short survey or tombstone))
Web of Science	("World Health Assembly"[Title/Abstract] OR WHA[Title/Abstract]) AND (resolution[Title/Abstract]) AND (transparen*[Title/Abstract] OR disclos*[Title/Abstract] OR disaggregat*[Title/Abstract] OR granular*[Title/Abstract] OR ambigu*[Title/Abstract]) Exclude: Document types: Book Review OR Editorial Material OR Meeting Abstract OR Meeting Summary OR Proceedings Paper OR Review OR Letter OR Note OR Correction

Appendix 2. **All sources included in the literature review**

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Agarwal & Gaule 2022	OOP expenses partial (CTs)	Industry total	clinicaltrials.gov; WHO COVID-19 candidate vaccine landscape database	COVID-19 vaccines and antiviral drugs			N	N	Industry, international organisations (WHO), governments, investors and funders, patients
AIM. International Association of Mutual Benefit Societies 2021	Y	Any expense incurred through to the regulatory approval: direct (or 'out-of-pocket') and indirect (royalties, buyout etc.) R&D, costs for pre-clinical and clinical development and all expenses related to R&D up to registration; also, for new indications	The best possible knowledge; a robust methodology to calculate medicines cost structures	To develop a comprehensive, open and transparent debate for a paradigm shift in the pricing of medicines. The need for transparency of medicines prices and cost structures is highlighted, especially for R&D and production costs, together with the development of a methodology to define those costs.	For the EC to analyse how a fair pricing model could be applied into the legal and regulatory framework: could be used along with the central registration at EMA level. EMA could be a one-stop shop to collect all necessary data to calculate fair medicines prices. The EC and HTA bodies could process this data and calculate a fair price.	Using a simple and transparent algorithm, the European fair price would cover the costs of research and production, also allow a justified but limited amount of expenditure on sales and medical information, offer reasonable profit, and grant a significant bonus for medicines with an added therapeutic value. The model aims to cover the real costs incurred by companies and to reach transparent price setting for new innovative medicines or new indications.	To incentivise companies' investments in R&D on in-house new molecules, rather than on high-priced buyouts of other companies.	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Allmending-er, Simaria, Turner & Farid 2014	OOP expenses total	Industry total	Farid, S.S., J. Washbrook & N.J. Titchener-Hooker, Modelling Biopharma-ceutical Manufacture: Design and Implemen-tation of SimBiopharma. Computers & Chemical Engineering, 2007. 31: p. 1141-58	Monoclonal antibod-ies (mAbs)			N	N	Industry
Amore 2020	N				Regulator and industry	Clearer accounting guidelines. US GAAP (accounting guidelines) states that firms must report R&D expend-iture in accounting documents. It does not provide clarification regarding how exactly to report in cases where there is no R&D.	For other firms, they can make more competitive decisions based on disclosed information. For the firm disclosing, they can be seen as more trust-worthy.	Rival firms can use information in a predatory way. Weak enforceability of require-ments to report information because report-ing outlays as operational or R&D expenses is discretionary. Joint R&D con-ducted by two separate firms is often less detailed and can mask relevant information as firms may view separate reporting as necessary.	Other firms, Securities and Exchange Commission

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Årdal & Røttingen 2012	N				Research	Provide initial funding for projects that utilise open-source data. Include all raw virtual and laboratory data in publications, so that anyone with knowledge on the subject could review and verify the data. Ensure project data is accessible, for example through Google searches and publicly available forums.	Content can be verified. There would be reduced costs for projects (It will be possible to de-link the cost of R&D and the cost of end product). Neglected diseases in particular, which have no cost incentive, might be cheaper to investigate.	Data may be used by others to patent and therefore profit from a drug they did not spend R&D on.	Researchers from the 'Global South', with fewer funding opportunities, researchers on projects that are studying neglected or rare diseases.
Årdal & Røttingen 2015	N				Research	Provide information about failures. Register projects before funding is provided. Make a registry of current projects in the field that is available to researchers. The registry should include summary of project; contact information for the researchers; identification of the donor, funder, or financing agency; links to the project website or other resources; keywords to help users locate the project when searching in a search engine; and a categorisation of which pharmaceutical value chain stage the research is in.	Leads to a reduction in duplicative research. Leads to more collaboration.	Not in line with intellectual property	Research groups, potential project collaborators, research funders

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Barel & Boman 2020	Y	Industry-reported data (DiMasi); unique data from non-profit drug development initiatives (e.g. DNDi); proprietary databases. Sertkaya et al. (Analytical Framework for Examining the Value of Antibacterial Products, 2014. US Department of Health and Human Services, p. 14-25) used Medidata Solutions; publicly available data (the US Food and Drug Administration's Drugs@FDA database, the NIH's ClinicalTrials.gov, the US Patent and Trademark Office's Patent and Full-Text Database (PatFT), filings with the US Securities and Exchange Commission (SEC), publications available through Medline, and other Internet-based resources. Light et al. (Light, D.W., J.K. Andrus, and R.N. Warburton, Estimated Research and Development Costs of Rotavirus Vaccines. Vaccine, 2009. 27(47): p. 6627-33), for instance, used PatFT, SEC filings, Medline, periodicals, and corporate websites to make estimates on the R&D costs of rotavirus vaccines. Wouters et al. (Wouters, O.J., M. McKee, and J. Luyten, Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA, 2020. 323(9): p. 844-53) analysed data from the SEC, Drugs@FDA database, ClinicalTrials.gov, and published data on clinical trials success rates).	Focuses on identifying NIH funding	Pharmaceutical companies using the high cost of R&D to justify high drug prices. In response to this argument, requests could be made for the numbers. Authors argue that there are reasons to disbelieve the narrative that high R&D costs are the reason for high prices.			Better understanding of the true costs of trials and identification of the primary drivers of the increase in the costs of clinical trials over time This might assist with making clinical trials more efficient - buyers might have a better negotiating position. Innovation and competition can direct R&D activity where the need is more urgent.	Administrative burden associated with additional reporting. Cost information on NIH-funded clinical trials is a trade secret or confidential commercial information. Disclosure of costs could harm the competitive position of drug developers.	Industry, payers, legislators, policymakers

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Battelle Memorial Institute 2015	OOP expenses partial (CTs)	Industry total	Tufts Center for the Study of Drug Development; ClinicalTrials.gov; Annual Fair Market Value (FMV) Survey published by Cutting Edge Information	All potential new medicines in some stage of CTs in the USA (not specified beyond that)			N	N	Industry, government, academia, non-profit organisations, patient advocacy groups, healthcare providers, patients
Berdud, Drummond & Towse 2020	OOP expenses total; OOP expenses partial (pre-CTs, CTs); cost of capital; attrition rate	Industry total for orphan vs. non-orphan drugs, and oncology vs. non-oncology drugs	R&D cost of a new medicine: Mestre-Ferrandiz et al. (Mestre-Ferrandiz, J., J. Sussex and A. Towse, The R&D Cost of a New Medicine, 2012, Office of Health Economics). Per-patient cost of clinical trials: Battelle Memorial Institute for Pharmaceutical Research (Battelle Technology Partnership Practice, Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies, 2015) and Pharmaceutical Manufacturers of America ultimately used Tufts Center for the Study of Drug Development. Authors collected data on probability of success from the BioMed Tracker, Pharmapremia database for the period 9/2009–9/2019	Any FDA-listed drug approved in 2015, further divided based on whether it is orphan or non-orphan and oncology or non-oncology.			N	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Brown & Martinsson 2019	N	Country total	Compustat database		Policymakers; industries affected by information environment	Reform security market	Reduces information asymmetries, decreases cost of arm's length financing; encourages innovative investments because R&D is information sensitive.	Competitive disadvantage due to information sharing to competitors. Costs of transparency would be higher for firms that can afford R&D without arm's length financing.	Policymakers
Bushman, Piotroski & Smith 2004	N/A – article is not specifically about R&D costs	N/A – article is not specifically about R&D costs	Information on financial statements of firms across the world from Center for International Analysis and Research. International Accounting and Auditing Trends, 4th ed. Princeton, NJ: CIFAR Publications, 1995.	N/A – article is about corporate transparency more broadly	Transparency stated to be the availability of firm-specific information to those outside publicly traded firms. They provide a theoretical perspective on how to conceptualise and measure transparency.	Improve the quality of information systems. This would include'high-quality financial reporting, financial analysts, institutional investors, and what they term as 'well-developed media channels'.	N	N	Industry, government, accounting bodies and specialists, investors, the media
Chen, Gu & Luo 2022	N		Wind Database of Chinese firms' R&D expenditure		Academic	Institutional support from regulators that make it conducive to disclose R&D information; focus on mandatory instead of voluntary disclosure.	Positive relationship between R&D expenditure disclosure and number of patents a firm has in emergent markets, such as China, more transparency may be linked to better institutional protection of intellectual property.	High market competition intensity means less likelihood firms will disclose R&D information.	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Chita, Parkera, Halperinb, Papadimitropoulosa, Krahna & Grootendorsta 2014	OOP expenses partial (CTs)	Industry total (Canada only)	DiMasi, J.A., et al., Cost of innovation in the pharmaceutical industry. Journal of Health Economics, 1991. 10(2): p. 107-42; Harrington, S.E. Cost of capital for Pharmaceutical, Biotechnology, and Medical Device Firms (13 November 2009); Trialtrove (database owned by Citeline intelligence solutions) available at SSRN: http://ssrn.com/abstract=1512938 or http://dx.doi.org/10.2139/ssrn.1512938; DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79. The cost of cost estimates for various inputs, such as the number of subjects: Canadian Center for Vaccinology, Dalhousie University, in Halifax, Nova Scotia, Canada. The cost of biopharmaceutical R&D: is biotech different? DiMasi JA & Grabowski H G, Managerial Decision Economics, 2007. 28: p. 469-79.	Seasonal influenza vaccine	Perspective of investors	Information about R&D costs should be made publicly available.	Improved decision making for investors if they know the costs of R&D; reduced uncertainty.	N	Investors, industry, the public

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Cole & Seabrook 2020	OOP expenses partial (CTs active Phases 2–3); attrition rate	Industry total for Alzheimer's disease drug development	Via Cummings et al. Cummings, J., et al., The Costs of Developing Treatments for Alzheimer's Disease: A Retrospective Exploration. Alzheimer's & Dementia, 2021. 18: p. 469-77.), which is in this table. Cost of failures of drug development from Scott et al. (Scott, T.J., et al., Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34)	All 'disease-modifying therapeutics'			N	N	
Cummings, Reiber & Kumar 2018	OOP expenses	Industry total for Alzheimer's disease drug development	Capitalised and including cost of failures of drug development from: Scott et al. (Scott, T.J., et al., Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34)	New drug treatments for Alzheimer's disease			N	N	Government, industry, venture capital, foundations, philanthropy (funders), patients
Cummings, Goldman, Simmons-Stern & Ponton 2021	OOP expenses: partial (CTs Phases 1–4); cost of capital; attrition rate	Industry total for agents with potential action in Alzheimer's Disease	Estimates for trial costs: Scott et al. (Scott, T.J., et al., Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34)	Any agent (defined as interventions by disease targets, e.g., circuits and synapses, amyloid beta, Tau, immunity and inflammation, other) with potential action in Alzheimer's disease			N	N	

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Darrow & Light 2021	N/A				Perspective of the public	Information to be made public by pharmaceutical companies includes: how much the public pays to manufacturers of drugs through indirect subsidies, incentives, tax credits and post-approval support. For costs which cannot easily be measured by manufacturers, legislators could direct the Government Accountability Office or the Centers for Medicare and Medicaid Services to look into the direct and indirect public funding of specified drugs.	Could inform future resource allocation decisions; and lead to access to better-priced drugs for patients and a "more ethical" drug development process.	N	Patients, payers, policy-makers
Daske, Hail, Leuz & Verdi 2008	N/A				Discussion is about the role of mandatory IFRS reporting in 26 countries	Mandatory or voluntary reporting	Positive liquidity and valuation effects for firms.	N	Industry, government, regulators, auditors, investors
Dinh, Schultze, List & Zbiegly 2020	Unclear	Industry total (Germany only)	Information provided within the German financial disclosure system (GAS 15)		Financial disclosure systems	R&D disclosures should be more comprehensive	R&D expenditure is important in estimating the firm's future performance. The information is also useful for investors who want to manage uncertainty.	N	Investors, industry, government

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DNDI, undated	Y	DNDi's direct OOP expenses per phase of development	DND's own projects: eight R&D projects, seven of which are treatments that are already registered and one of which is in late-stage development	Treatment (but they refer to three types: existing drugs without new formulation; existing drugs with new formulation; new chemical entities)	As part of DNDI's commitment to cost transparency, to promote accountability and fair pricing	Publish own estimates	Credibly inform a review of drug R&D costs under its virtual, collaborative model. R&D cost transparency is an important matter of accountability for any institution that benefits from public and philanthropic support for development of health tools for neglected populations.	N	
Durisch (The Berne Declaration / Health Action International) 2015	N				Takes perspective that the high private sector costs of R&D may be a 'myth' because the public sector now has a more direct role in the applied-research phase of drug discovery. Questions whether the public sector's share is fully taken into account in the industry R&D estimates.		Independence, transparency and accountability of decision-making processes and bodies.	N	
EC, European Pharma Strategy 2021	N					Working with European Union countries on non-legislative ways to improve transparency, such as guidelines on how to calculate the R&D costs of medicines for 2021–2024.	Better understanding and greater clarity are required as a basis for policy debates on the pricing of niche medicines and 'fair return' on research contributions.	N	

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Farid, Baron, Stamatis, Nie & Coffman 2020	OOP expenses total; OOP expenses partial (pre-CTs, CTs, post-CTs); cost of capital; attrition rate	Industry (modelled) totals for three different scenarios: worst-, average and best-case scenarios of different phase success rates	Cost of failures of drug development from: Scott et al. (Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34). To estimate total workload required for process development that considers FTE salary overheads of on-costs, management and for success rates of monoclonal antibodies, used: Kaplon H & Reichert JM. Antibodies to watch in 2019. Mabs, 2019;11(2):219-38. Infrastructure, used: Hassan et al. (Hassan, S., et al., Process Change Evaluation Framework for Allogeneic Cell Therapies: Impact on Drug Development and Commercialization. Regenerative Medicine, 2016. 11(3): p. 287-305). For biopharmaceutical costs of R&D in general, used: DiMasi & Grabowski (DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79).	Biopharmaceuticals and monoclonal antibodies			N	N	

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Fletcher 2019	N				Comments on the WHA resolution, saying that it is an important first step in making markets more transparent, and is the beginning rather than the end of a process.	Notes that the WHA resolution creates a mandate for member states and the WHO to create systems to collect and share information about prices, sales, units sold, patents, public and private sector R&D costs and R&D subsidies.	N	N	
Francis, Huang, Khurana & Pereira 2009	N/A				Authors follow Bushman, R.; J. Piotroski; and A. Smith. What Determines Corporate Transparency *Journal of Accounting Research* **42** (2004): 207– 52 Bushman et al. 2004 definition of corporate transparency as 'the availability of firm-specific information to those outside publicly traded firms'.		Better resource allocation within countries, because transparency: improves firms' access to lower cost external financing; contributes to more informative stock prices; and allows greater monitoring by outside investors.	N	Financial institutions, industry, government, investors
Frank & Hannick 2022	Review of literature				The research uses a variety of methods that, in turn, produce a wide range of estimates; thus, the simple comparison of estimates can result in misleading judgements.				
Franssen (PPE) 2020	N					Notes that the Pharmaceutical Strategy for Europe has set out actions to ensure affordability of medicines for patients and health systems' financial and fiscal sustainability.	Better understanding and greater clarity on aspects of national competence, such as pricing mechanisms.	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Global Alliance for TB Drug Development 2001	Costs of successfully developing a new chemical entity (NCE) for TB have been estimated.	The costs of developing a new chemical entity to treat TB include the value of the purchased resources plus the value of company-owned resources employed in the effort and the costs of failures.	TB Alliance's own data	NCE candidates within TB Alliance portfolio			N	N	
Gupta Strategists 2019	Y Top-down model of the average R&D cost per new molecular entity	Reports on studies in literature, which in turn use R&D cost data at different levels	From the literature	New molecular entity			N	N	
Hassan, Huang, Warren, Mahdavi, Smith, Jong & Farid 2016	OOP expenses total; cost of capital	Unclear	Made own assumptions about cost of FTE salary and other overheads	Allogeneic cell therapies			N	N	Biopharmaceutical industry, patients
Hay, Thomas, Craighead, Economides & Rosenthal 2014	OOP expenses total; cost of capital; attrition rate	Industry total (based on 835 companies)	BioMed Tracker database (uses 'information from company press releases, analyst conference calls, and presentations at investor and medical meetings' p.41)	NMEs and biologic licence applications (BLAs)			N	N	Industry, regulators, policymakers, patients

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
't Hoen 2019	N				Reports discussion around WHA resolution. Calls for transparency emerged as the central theme with regard to medicines pricing, production cost and expenditures on R&D.	One successful example put forward is the Drugs for Neglected Diseases Initiative (DNDi), which is open about its R&D outlays.	N	N	64 civil society organisations published a statement before the meeting calling for greater medicines pricing and R&D cost transparency.
Laplante, Skaifeb, Swensonc & Wangerin 2019	OOP expenses total	Industry total	Compustat database and own calculations			Pharmaceutical companies should share information about how much was invested in R&D.	Decreased burden on tax regulators and auditors.	N	Pharmaceutical companies, government, IRS and tax practitioners, the public
Li & Rizzo 2020	OOP expenses total	Industry total for top-selling drugs	Compustat database	All 13 BlueCross-and BlueShield-classified therapeutic classes (e.g., anti-infective drugs, cancer drugs, genitourinary drugs, gastrointestinal drugs, pain relief drugs, etc.)			N	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Lilliu 2019	N			Unclear	Discusses US bill to introduce a requirement for pharmaceutical companies to publish R&D costs of some medicines, to inform negotiation of prices paid by Medicare. Comments that in France a bill mandating manufacturers to communicate to France's Drug Price-Setting Committee (CEPS) how much public funding they received throughout their product R&D, was adopted.		Improve the transparency of R&D funding across the value chain.	N	
Love 2016	N			Unclear	Notes that the most important data to have in detail are the outlays on specific clinical trials, and the number of patients in each trial. From those two figures, can be calculated the per-patient costs of the trials, and that can be used to check the validity and reasonableness of the self-reported figures, and also to model the costs for other drug development projects.	Asserts that government policies requiring more disaggregated disclosure are needed.	To make better decisions about drug pricing, incentive mechanisms and funding of R&D.	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Médecins sans Frontières 2022	N				The report states that there is a call for the US government to require transparent costs of clinical trials. They report that pharmaceutical corporations justify charging high prices for medicines, vaccines and tests by saying that it costs billions to bring a drug to market, but that it is not possible to know how truthful these claims are because companies do not disclose how much they actually spend on R&D for each medicine.	Authors state that clinical trials are the most expensive part of bringing a drug to market, so if these costs were made public then, they argue, that would enable fair prices to be negotiated.	Authors argue that forcing pharmaceutical corporations to share the costs of all clinical trials could lead to 'fairer' prices and better patient access to medicines.	N	
Mittra, Bruce, Scannell & Tait 2021	OOP expenses total; cost of capital; attrition rate	Industry total	Sertkaya, A., et al., Analytical Framework for Examining the Value of Antibacterial Products, 2014. US Department of Health and Human Services, p. 14-25. (included in Schlander, M., K. Hernandez-Villafuerte, C.-Y. Cheng, J. Mestre-Ferrandiz, and M. Baumann, How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. Pharmacoeconomics, 2021. 39(11): p. 1243-69.)	Antibiotics for hospital-acquired pneumonias (VABP/HAPB) and community-acquired pneumonias (CAP)			N	N	Pharmaceutical industry, innovation communities, policymakers and regulators, hospitals, patients

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Moore, Heyward, Anderson & Alexander 2020	OOP expenses partial (CTs)	Industry total	2015–2017 annual reports on novel drugs published by the FDA's Center for Drug Evaluation and Research; clinicaltrials.gov; drugs@FDA; derived the estimates for each trial using the IQVIA CostPro Mid-Level Tool (trial sites in 60 countries). For each trial, the 'CostPro' produced a low, median and high estimate based on industry benchmark data. The tool 'estimates were derived from actual data from 2000 final awarded trial proposals and they integrate cost information from 200,000 trial sites in 60 countries p.2	New therapeutic agents	Perspective of industry (with regards to the complexity of regulatory systems)	Authors argue that pharmaceutical companies should make information on patient engagement during clinical trials public to allow an understanding of whether current practices are cost effective and feasible.	Authors believe that this information is crucial to assess whether current new drug authorisation regulation is too burdensome and costly.	N	Pharmaceutical companies, government, regulators, investors, the public
OECD 2018	N				Strengthen the information base to better inform policy debates. Despite the complexity of assessing with precision the costs incurred in successful and unsuccessful product development, both payers and the general public need a better understanding of the costs involved in developing new medicines, how these costs are incurred, and the magnitude of the returns investors and companies earn from these activities.	Publishing authoritative information on industry activities and the risks, costs and returns from R&D.	To better inform policy decisions.	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Perehudoff 2022	N					Notes that two European governments (France, Italy) have adopted laws requiring pharmaceutical manufacturers to disclose the public R&D investments in new medicines seeking reimbursement.	Openness about a medicine's price components, including R&D costs, is argued to be essential to know whether the price is 'fair' to the seller and the buyer.	If R&D cost transparency undermines differential pricing between countries that could lead to low-income countries having to pay higher prices.	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Perehudoff, Mara & 't Hoen 2021	N				The authors discuss how high prices can create inequities within and among EU member states and lead to unacceptable levels of OOP expenditure in countries of all income levels. They state that an obstacle to addressing this problem is lack of transparency around the cost of R&D and the prices of health products.	The authors state that they didn't identify any mechanisms to improve the transparency of R&D costs and better understand their relationship to price. They suggest that the WHO Regional Office for Europe could play a key role in supporting member states to implement resolution WHA72.8, which they state might be done in association with WHO collaborating centres and/or the research community. Suggest creating a framework to survey existing and proposed national legislation on medicines cost and price transparency in all EU member states. Also suggest creating a public repository of all transparency data related to medicines markets to support the regular monitoring and evaluation of legislative proposals and their implementation in practice. Examples of best practice could be collected regarding which data types are disclosed and which legal strategies are used to achieve disclosure.	Fairer medicine prices. Authors refer to WHO's working definition of a fair price as one that is affordable for both health systems and patients and, at the same time, provides sufficient market incentive for industry to invest in innovation and the production of medicines. Also argue that better-informed procurement processes may lead to better allocation of public resources and that market inefficiencies resulting from information asymmetry could be reduced. Also suggest that R&D cost data could be used to improve the focus of research efforts, including those supported by public financing.	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Rennane, Baker & Mulcahy 2022	OOP expenses total; cost of capital; attrition rate	Various, as per literature	Literature review	All new drugs, new molecular entities, and drugs in specific therapeutic classes	Investors and policymakers are interested in this information	Information that should be made transparent includes R&D timelines involved to bring new drugs to market; direct (e.g. supplies) and indirect (e.g. overhead expenses) costs; the time value of R&D investments; and the costs of abandoned projects.	Improved decision making by investors; enabling policy that would regulate drug prices.	N	Industry, government, the public, investors, academia
Roediger, Chair, Oncology Platform of the European Federation of Pharmaceutical Industries and Associations, 2019	N				Transparency is a prominent topic in the healthcare debate, particularly related to pharmaceutical policy. There is a need for transparent prices, and more transparency in research and development costs, patents and clinical trials, and for declaring how much public funding has gone into medicines development.		Clarity, good governance and better understanding.	May expose an inventor unnecessarily, making his or her invention accessible to, and copiable by, everyone. That could deter inventors from investing the time and money.	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Schlander et al. 2021	OOP expenses total; OOP expenses partial (pre-CTs, CTs, post-CTs); cost of capital; attrition rate	Various, as per literature	Literature review	NMEs	Studies based on the database created by the Tufts Center for the Study of Drug Development are particularly criticised. The controversy stems from the magnitude of the estimates and the alleged close relationship the Tufts Center has with the pharmaceutical industry. The debates around the Tufts' studies, which also apply to other studies, centre on four issues. First, the transparency and the breadth of coverage of data used are called into question given the data are shielded from external scrutiny. Second, results might be overestimated because the focus is on self-originated NMEs, which may cost more. Third, some critics argue that the cost of capital applied is too high. Fourth, the estimates may not fully recognise that drug R&D activities receive a considerable amount of public funding. The authors from the Tufts group have countered these criticisms, defending the representativeness of their samples, the use of opportunity costs, the reasons for focusing on self-originated NMEs, and for their exclusion of public funding. But ultimately their results cannot be substantiated.	'In this regard, our framework can serve as a guideline of the minimum set of factors that should be considered in future R&D cost estimations. If some proposed factors are not taken into account, they should at least be discussed in terms of the potential effects on the estimation. There remains a long way to the establishment of a commonly agreed framework to evaluate R&D cost estimations, particularly when considering that the R&D of new molecular entities is far from static. We believe our framework can play an important role in providing clarity on what a particular R&D cost estimation captures' (p. 1266).		'However, proposals for increased transparency of R&D costs face practical difficulties. for instance, accounting for the actual cost may remove incentives for manufacturers to accelerate and efficiently manage development. Furthermore, it may be challenging to obtain the desired transparency (e.g., the actual cost of failures)' (p.1265).	Pharmaceutical industry, patient groups, policymakers, researchers

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Sengupta 2016	N						N	Industry profits and social welfare are lower when there is transparency between strategically competing pharmaceutical companies.	Industry, government
Silverman E, 2016	N				Discusses a call for cost transparency in the pharmaceutical industry.	The Sunshine Act provision of the Affordable Care Act, which requires companies to provide data on payments made to doctors and put them in a publicly accessible federal database, has set a precedent for disclosing proprietary information.	Lower prices to be negotiated for some Medicare medicines.	After US President Obama outlined his plans, the pharmaceutical industry trade association in the USA issued a statement arguing that they would stifle innovation, and that they failed to take into account either the cost of R&D failures or the long-term value that medicines provide.	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Simoens & Huys 2020	OOP expenses total; cost of capital; attrition rate	N/A	Literature review	All new medicines	Research community	Considers there is a need to systematically provide estimates of individual cost components in future studies with a view to examine the relative importance of cost components and how their importance evolves over time. It is also necessary to improve the methodologies that exist to attribute costs of discovery and preclinical development to individual medicines.	More information on R&D costs could give insight into R&D productivity and how this could be improved.	N	Industry, research community

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Thomson Reuters 2020	N				Discusses new US federal legislation. The bill aimed to amend the Securities Exchange Act of 1934 directing the SEC to issue rules requiring the disclosure in annual reports of total R&D expenditures on drugs that includes disaggregated basic research, pre-clinical research, Phase I, II, and III clinical investigations, and post-market studies or clinical trials. It excluded the cost incurred in connection with licensing agreements or acquiring intellectual property; costs of mergers or acquisition; certain intangible costs; and the estimated COC, according to the bill text.	House and Senate Democrats on 7 April 2022 introduced legislation requiring publicly traded drug makers to make new disclosures around R&D costs, including for clinical trials broken out by phase. The Pharmaceutical Research Transparency Act of 2022 is stated to form part of a broader package of bills targeting the pharmaceutical industry.	To strengthen competition and promote innovation.	N	
Tsourougiannis 2017	N				Perspective from within a pharmaceutical company	Pharmaceutical companies should report costs of R&D transparently within the company using a bespoke online pricing and reimbursement tool.	Improved price visibility and transparency across the company.	N	Industry

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
van der Schans, De Loos, Boersma, Postma & Büller 2022	OOP expenses total; cost of capital; attrition rate	Industry total	The Evaluate Pharma database; Prasad, V. and S. Mailankody, Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. JAMA Internal Medicine, 2017. 177(11): p. 1569-75), included in Schlander et al. (Schlander, M., K. Hernandez-Villafuerte, C.-Y. Cheng, J. Mestre-Ferrandiz, and M. Bauman, How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. Pharmacoeconomics, 2021. 39(11): p. 1243-69)	NMEs		Improved public–private collaborations	N	N	Governments, authorities, public institutions, pharmaceutical industry, investors (through subsidies, grants, universities and hospitals), patients

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Vogler 2022	N	Several publications on R&D costs are cited.			R&D, production and marketing costs are stated as opaque, including the share of public funding involved. Costs for clinical trials and further R&D-related activities conducted by pharmaceutical companies are not publicly accessible, neither are input cost data for R&D per medicine accessible to governments. Some countries' authorities require these data from the companies as background information for pricing and reimbursement decisions.	It is argued that information on input cost data would provide valuable background information to price negotiations, even if medicine prices are not based solely on cost data. The 2019 legislation in Italy stipulates an obligation for the company to communicate marketing costs and any discrepancies with what had previously been defined. In Ireland, input cost data can be requested by the Health Service Executive in cases where viability and sustainability of supply is a concern. The data are not made publicly accessible. There are also examples in Spain and Italy.	Transparency is important for good governance and accountability, and to support evidence-based policy making. Transparency could also support pricing policies. Limited transparency is discussed as being potentially detrimental to effective policy decision making. Cost input factors – including R&D and production costs and marketing expenses are put forward as instructive background information that public authorities can consider in their appraisals of pricing and reimbursement requests from pharmaceutical companies.	N	

Paper – Authors and year	R&D cost data reported? (y/n)	R&D cost data level	Ultimate source of cost data reported	Scope of definition of 'medicine' adopted	Discussion of transparency of R&D cost per medicine and perspective taken	Proposed actions for achieving greater transparency	Expected advantages of greater transparency are stated (y/n)	Expected disadvantages of greater transparency are stated (y/n)	Stakeholders mentioned
Wang & Fan 2014	OOP expenses partial (CTs); cost of capital	Industry total (China only)	Sources publicly available in China	Unclear	Perspective of investors		Transparency enables investors to make informed decisions on business innovation capability and development plans.	N	Industry, government
WHA Resolution 2019	N				The resolution seeks to 'progressively enhance the publicly available information on inputs across the value chain of health products, the public reporting of the relevant patents and their status, and the availability of information on the patents landscape covering a particular health product as well as its marketing approval status.'	The resolution seeks to 'take the necessary steps, as appropriate, to support dissemination and enhanced availability of, and access to, aggregated results data and, if already publicly available or voluntarily provided, costs from human subject clinical trials regardless of outcomes or whether the results will support an application for marketing approval, while ensuring patient confidentiality.	N	N	
Wouters, Berenbrok, He, Li & Hernandez 2022	OOP expenses total; cost of capital; attrition rate	Industry total	Wouters OJ, McKee <D and Luyten J, estimated research and development investment needed to bring a new medicine to market, 2009-2018, JAMA 2020l 323(9): 844-853	63 new drugs approved by the FDA	Perspective of the public and policymakers	Pharmaceutical companies should make more data available to the public – especially if they continue to argue that R&D costs justify high medicine prices.	Being able to understand drug pricing and relationship of pricing to costs incurred by the pharmaceutical industry.	N	Pharmaceutical industry, policymakers, the public

Appendix 3. **Sources of estimates from the literature review**

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
Adams & Brantner 2006	Both	Phase level. DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85	CAPM, DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85.	Own estimation based on Pharmaprojects
Adams & Brantner 2010	Both	Phase level. Compustat and Global Vantage Industrial Commercial	CAPM, DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85	Collected data and compared data with Adams, C.P. and V.V. Brantner, Spending on New Drug Development. Health Economics, 2010. 19(2): p. 130-41
Agarwal & Gaule 2022	Neither	Partial: CTs. Stated (and ultimate) source: Annual Fair Market Value (FMV) Survey published by Cutting Edge Information	Not stated	Not stated
Allmendinger, Simaria, Turner & Farid 2014	Neither	Partial: raw materials used in CTs. Stated (and ultimate) source: Farid SS, Washbrook J and Titchener-Hooker NJ, Modelling biopharmaceutical manufacture: design and implementation of SimBiopharma. Comput Chem Eng 31:1141–1158 (2007)	Not stated	Not stated
Årdal et al. 2018	Schlander et al. 2021	Survey of European small to medium-sized enterprises (based on existing studies)	Not considered	Not considered
Battelle Memorial Institute 2015	Neither	Partial: CTs. Stated (and ultimate) source: Annual FMV Survey published by Cutting Edge Information (CEI)	Stated (and ultimate) source: Tufts Center for the Study of Drug Development	Not stated

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
Berdud, Drummond & Towse 2020	Neither	Total and partial. Stated sources: OOP was estimated by multiplying average number of patients in clinical trials and per-patient costs. Data on the probability of success was taken from the Biomed Tracker, Pharmapremia database for the period 9/2009–9/2019Per-patient cost of clinical trials: Battelle Memorial Institute for Pharmaceutical Research and Manufacturers of America (Battelle Memorial Institute. Biopharmaceutical industry-sponsored clinical trials: impact on state economies. 2015. http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf. Accessed 9 Oct 2018). Ultimate source: Tufts Center for the Study of Drug Development. Briefing: Cost of Developing a New Drug, November 18, 2014. CSDD & Tufts School of Medicine.	Stated source: R&D cost of a new medicine: Mestre-Ferrandiz et al. 2012 (Mestre-Ferrandiz, J., J. Sussex and A. Towse, The R&D Cost of a New Medicine, 2012, Office of Health Economics. https://www.ohe.org/publications/rd-cost-new-medicine. As of 27 January 2023). Ultimate sources: DiMasi et al. 2016 (DiMasi, J.A., H.G. Grabowski, and R.W. Hansen, Innovation in the Pharmaceutical Industry: New Estimates of R&D costs. Journal of Health Economics, 2016. 47: p. 20-33.) and Paul S.M., Mytelka D.S., Dunwiddie C.T., Persinger C.C., Munos Lindborg S.R., Schacht A.L.. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9:203–14. doi:10.1038/nrd3078. Paul et CAPM based on DiMasi et al. 2003 (DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85)	Stated (and ultimate) source: Biomed Tracker, Pharmapremia database for the period 9/2009–9/2019
Brown & Martinsson 2019	Neither	Not stated	Country total. Stated (and ultimate) source: Compustat database	Stated (and ultimate) source: Compustat database
Chen, Gu & Luo 2022	Neither	Total. Stated source: Data using accounts at the company level and a Chinese database on macroeconomies and industry (WIND)	Not stated	Not stated
Chit et al. 2014	Both	Component level (CCfV). Trialtrove database: quality of inputs required to produce a new drug. Discovery and preclinical: DiMasi et al. The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics. 2003;22(2):151-185	CAPM; Fama-French: Harrington, S.E.. Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms. In Danzon, P.M. & Nicholson, S. (Eds.), *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, 2012; (pp. 75-99). New York: Oxford University Press. DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79	Own estimation based on Trialtrove database
Cole & Seabrook 2020	Neither	Partial: CTs, active Phases 2–3. Stated (and ultimate) source: Via Cummings et al. 2018, which is in this table (Cummings, J.L., C.L. Reiber, and P. Kumar, The price of Progress: Funding and Financing Alzheimer's Disease Drug Development. Alzheimer's & Dementia; Translational Research & Clinical Interventions, 2018. 4: p. 330-43). Ultimate sources: Phase level: SEC filings, annual 10-K and quarterly 10-Q forms. Discovery & preclinical: Costs tracked from the year a company started reporting costs. Assumed preclinical and clinical costs incurred during initial development included in licensing fees and milestone payments.	Stated (and ultimate) source: CAPM: DiMasi et al. (DiMasi, J.A., H.G. Grabowski, and R.W. Hansen, Innovation in the Pharmaceutical Industry: New Estimates of R&D costs. Journal of Health Economics, 2016. 47: p. 20-33)	Stated (and ultimate) source: Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34. Ultimate source: Phases 1–3: Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics*. 2019;**20**(2):273-286. doi: 10.1093/biostatistics/kxx069 Proportion of biologics licence applications and new drug applications approved by the FDA

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
Cummings, Reiber & Kumar 2018	Neither	Total. Stated (and ultimate) source: Scott et al. (Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34)	Stated (and ultimate) source: Scott et al. (Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34)	Stated (and ultimate) source: Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34
Cummings, Goldman, Simmons-Stern & Ponton 2021	Neither	Partial: CTs, Phases 1-4. Stated (and ultimate) source: Scott et al. 2014 (Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34), who used DiMasi et al. 2003 (DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85) and DiMasi & Grabowski 2007 (DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79)	Stated source: Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34). Ultimate sources: DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79) (11%); Paul et al. 2010 (Paul S.M., Mytelka D.S., Dunwiddie C.T., Persinger C.C., Munos Lindborg S.R., Schacht A.L.. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9:203–14. doi:10.1038/nrd3078)	Stated (and ultimate) source: Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34. Scott et al. conducted expert consultations for transition probabilities including potential outcomes of Alzheimer's disease investment and the probabilities of having a disease-modifying drug for AD on the market.
DiMasi & Grabowski 2007	Both	Phase level. CSDD survey of 10 pharmaceutical companies and separate biotech firm Discovery and preclinical annual expenditures split into pre-human and clinical periods Discovery and preclinical: DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85.	CAPM, Myers, Shyam-Sunder method (1995) (Myers SC, Shyam-Sunder L. 1995. Measuring pharmaceutical industry risk and the cost of capital. In: Helms RB (Ed.). Competitive Strategies in the Pharmaceutical Industry. Washington, DC: American Enterprise Institute for Public Policy.)	Own estimations based on the Tufts CSDD database
DiMasi et al. 1991	Both	Phase level. Tufts CSDD survey of 12 pharmaceutical companies	CAPM, Grabowski & Vernon (1990) (Henry Grabowski, John Vernon, (1990) A New Look at the Returns and Risks to Pharmaceutical R&D. Management Science 36(7):804-821.)	Tufts CSDD database
DiMasi et al. 1995	Schlander et al. 2021	Confidential survey of 12 US pharma companies, TUFTS CSDD database	CAPM, DiMasi et al. (1991)	Tufts CSDD database
DiMasi et al. 1995	Schlander et al. 2021	Confidential survey of 12 US pharma companies, TUFTS CSDD database	CAPM, Grabowski & Vernon (1990) (Henry Grabowski, John Vernon, (1990) A New Look at the Returns and Risks to Pharmaceutical R&D. Management Science 36(7):804-821.)	Tufts CSDD database

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
DIMasi et al. 2003	Both	Phase level. Survey of 10 pharmaceutical companies)	CAPM, Myers, Shyam-Sunder method (1995) (Myers SC, Shyam-Sunder L. 1995. Measuring pharmaceutical industry risk and the cost of capital. In: Helms RB (Ed.). Competitive Strategies in the Pharmaceutical Industry. Washington, DC: American Enterprise Institute for Public Policy.)	Own estimations based on the Tufts CSDD database
DiMasi et al. 2016	Both	Phase level. CSDD survey of 10 pharmaceutical companies	CAPM, based on DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85	Own estimations based on the Tufts CSDD database
DiMasi et al. 2004	Schlander et al. 2021	Confidential survey of 10 pharmaceutical companies	CAPM, DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85	Own estimations based on the Tufts CSDD database
Dinh, Schultze, List & Zbiegly 2020	Neither	Unclear	Information provided within the German financial disclosure system (GAS 15)	Information provided within the German financial disclosure system (GAS 15)
DNDI, undated	Neither	OOP cost per phase for eight products (Drugs for Neglected Diseases Initiative (DNDI) own projects).	Not discussed	Unclear
Falconi et al. 2014	Schlander et al. 2021	Expert opinion; ClinicalTrials.gov FDA data	CAPM and Fama-Frech (F-F) models. Harrington, S.E. (2012). Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms. In Danzon, P.M. & Nicholson, S. (Eds.), *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, (pp. 75-99). New York: Oxford University Press.	Own estimations based on clinicaltrials.gov and FDA data
Farid, Baron, Stamatis, Nie & Coffman 2020	Neither	Total and partial. Stated (and ultimate) source: to estimate total workload required for process development that considers FTE salary overheads of on-costs, management and infrastructure, used: Hassan, S., H. Huang, K. Warren B. Mahdavi, D. Smith, S. Jong, and S.S. Farid, Process Change Evaluation Framework for Allogeneic Cell Therapies: Impact on Drug Development and Commercialization. Regenerative Medicine, 2016. 11(3): p. 287-305.. doi:10.2217/rme-2015-0034. For biopharmaceutical costs of R&D in general, used: DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79)	Capitalised cost calculated as the OOP cost adjusted for COC and to account for the time value of money. Stated (and ultimate) source: Paul et al. 2010 (Paul S.M., Mytelka D.S., Dunwiddie C.T., Persinger C.C., Munos Lindborg S.R., Schacht A.L.. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9:203–14.)– capitalised phase costs, assuming a COC of 11%.	Stated (and ultimate) source: Scott, T.J., J. Troy, A.C. O'Connor, A.N. Link & T.J. Beaulieu, Economic Analysis of Opportunities to Accelerate Alzheimer's Disease Research and Development. Annals of the New York Academy of Sciences, 2014. 1313: p. 17-34. For success rates of monoclonal antibodies, used: Kaplon et al. 2019 (Kaplon H, Reichert JM. Antibodies to watch in 2019. Mabs. 2019;11(2):219–38.).

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
Frank & Hannick 2022	Neither	The literature, primarily Schlander et al. 2021. In one of the most prominent estimation exercises, DiMasi & Grabowski (DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79) use data for costs and drug launches from a sample of 'Big Pharma' products. They reported mean and median capitalised R&D costs per new drug to be $2.6 billion and $1.9 billion, respectively, in 2013 US dollars, a 31% difference.	The literature. Several different user costs of capital assumptions. User COC parameters most often used are 10.5% and 11% (range 7%–11.5%). Time cost of money component of the capitalised costs accounts for between 35% and 51% of average capitalised costs of R&D. When a lower COC level of 7% was used, the time cost of money accounted for about 21% of the total.	References Schlander et al. (2021)
Gupta Strategists 2019		Not made explicit but appears to be the literature.	COC accounts for approximately half of total R&D costs per NME, in absolute terms 1.3 billion USD. Source: Not made explicit but appears to be the literature.	Not made explicit but appears to be the literature.
Global Alliance for TB Drug Development 2001	Both	Component level (expert elicitation): CDC, SAMRC, the Sequella Foundation and WHO PAREXEL's Pharmaceutical R&D Sourcebook Current procedural terminology code (American Medical Association) Discovery estimates: PhRMA Preclinical and microbiology test costs estimates: research organisations specialising in microbiology, toxicology, and drug metabolism Safety tests: M3 Guidance for Industry developed in the International Conference on Harmonisation (ICH)	Personal contact with H. Grabowski; Myers & Shyam-Sunder (1995) (Myers SC, Shyam-Sunder L. 1995. Measuring pharmaceutical industry risk and the cost of capital. In: Helms RB (Ed.). Competitive Strategies in the Pharmaceutical Industry. Washington, DC: American Enterprise Institute for Public Policy.); Myers & Howe (1997) (Myers SC, Howe CD. 1997. A Life Cycle Financial Model of Pharmaceutical R&D. Cambridge, Massachusetts: MIT Program on the Pharmaceutical Industry.).	Boston Consulting Group, 2000 (Boston Consulting Group. 2000. Global Alliance for TB Drug Development Business Plan. Presented at the Global Alliance for TB Drug Development meeting, Geneva, Switzerland. September)
Hanson 1979	Schlander et al. 2021	Costs, representing 0.2 billion USD in 2017. Most of these costs are incurred in Phase 3 trials	Different COC value tested, 8% rate	Survey
Hassan, Huang, Warren, Mahdavi, Smith, Jong & Farid 2016	Neither	These costs are driven by the trial size, i.e. the number of patients required to demonstrate effect	Unclear	Not stated
Hay, Thomas, Craighead, Economides & Rosenthal 2014	Neither	Not stated	Stated (and ultimate) source: BioMedTracker database (uses 'information from company press releases, analyst conference calls, and presentations at investor and medical meetings' p. 41)	Stated (and ultimate) source: BioMedTracker database (uses 'information from company press releases, analyst conference calls, and presentations at investor and medical meetings' p. 41)

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
Jayasyndara et al. 2013	Both	Participant	CAPM, based on DiMasi, J.A., H.G. Grabowski, and R.W. Hansen, Innovation in the Pharmaceutical Industry: New Estimates of R&D costs. Journal of Health Economics, 2016. 47: p. 20-33.	Transition probabilities from Hay, M., et al., Clinical Development Success Rates for Investigational Drugs. Nature Biotechnology, 2014. 32(1): p. 40-51
Laplantea, Skaifeb, Swensonc & Wangerin 2019	Neither	Total. Stated (and ultimate) source: Compustat and own calculations	Not discussed	Not discussed
Li & Rizzo 2020	Neither	Total. Stated (and ultimate) source: Compustat	Not discussed	Not discussed
Light & Warburton 2011	Rennane et al. 2021	Phase level. DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85		Not discussed
Light et al. 2009	Rennane et al. 2021	Component level (expert elicitation)	Not discussed	Not discussed
Mestre-Ferrandiz et al. 2012	Both	Phase level. CMRI survey of 16 pharmaceutical companies	CAPM, based on DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85.	Own estimations (based on CMRI data)
Mittra, Bruce, Scannell & Tait 2021	Neither	Tiers of approval taken from Sertkaya, A., et al., Analytical Framework for Examining the Value of Antibacterial Products, 2014. US Department of Health and Human Services, p. 14-25.	Tiers of approval taken from Sertkaya, A., et al., Analytical Framework for Examining the Value of Antibacterial Products, 2014. US Department of Health and Human Services, p. 14-25.	Tiers of approval taken from Sertkaya, A., et al., Analytical Framework for Examining the Value of Antibacterial Products, 2014. US Department of Health and Human Services, p. 14-25.
Moore, Heyward, Anderson & Alexander 2020	Neither	Partial: CTs. Stated (and ultimate) source: IQVIA CostPro Mid-Level Tool (in this tool 'estimates were derived from actual data from 2000 final awarded trial proposals and integrates cost information from 200000 trial sites in 60 countries. for each trial CostPro produced a low, median and high estimate based on industry benchmark data' p. 2)	N	N
Paul et al. 2010	Both	Phase level. Pharmaceutical Benchmarking Forum survey of 13 pharmaceutical companies and internal 15-year data from Eli Lilly; survey (PBF/KMR) – success rate and development time	CAPM, based on DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The Price of Innovation: New Estimates of Drug Development Costs. Journal of Health Economics, 2003. 22(2): p. 151-85.	Industry benchmarking study (PBF/KMR). Approximations based on Eli Lilly data and other public sources
Prasad & Mailankody 2017	Both	Firm level. SEC filings: SEC10-K	Buffett EC.(thestreet.com) and experts, based on normally paid by pharmaceutical companies and experts information	Not considered

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
Rennane, Baker & Mulcahy 2022	N/A	Stated. Source: the literature	Stated (and ultimate) source: The literature. Studies which include an estimate vary in their method: Estimated rate of return based on pharmaceutical bonds (1-5%), typical government investments (3–7%), the Capital Asset Pricing Model (10–11%) or a more flexible model to account for systematic risk (10–13%).	Stated (and ultimate) source: The literature. Authors discuss 'abandoned development projects' which typically divide the average phase costs by an estimate of the probability that a drug in a given phase will reach approval.
Schlander et al. 2021	N/A	Stated source: The literature	Stated source: The literature	Stated source: The literature
Scott et al. 2014	Rennane et al. 2021	Component level (expert elicitation)	Not discussed	Not discussed
Sertkaya et al. 2014	Schlander et al. 2021	Expert opinion. Submission costs: new drug application fee for drug or biologic products requiring clinical data. Cash expenses per investigational compound from DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79. Submission cost: new drug application fee for drug or biologic products requiring clinical trial. Discovery and preclinical: Paul et al. 2010 (Paul S.M., Mytelka D.S., Dunwiddie C.T., Persinger C.C., Munos Lindborg S.R., Schacht A.L.. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9:203–14.) (including ABX); DiMasi, J.A. and H.G. Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics, 2007. 28(4-5): p. 469-79 (including vaccines)	Previous articles and expert consultation	Previous studies and expert consultation
van der Schans, De Loos, Boersma, Postma & Büller 2022	Neither	Total. Authors calculated OOPs spent on a successful product using data from the Evaluate Pharma database: preclinical up to registration and Phase 4 investments, data on NMEs total R&D costs were derived from the literature	Evaluate Pharma database and the literature	Evaluate Pharma database and the literature
Wang & Fan 2014	Neither	Partial. CTs Sources publicly available in China	Sources publicly available in China	Unclear
Wiggins 1987	Schlander et al.	PMA annual survey and FDA approval data by therapeutic class	CAPM, Source not available online.	Not considered
Wouters, Berenbrok, He, Li &Hernandez 2022	Neither	Total. Stated source: Wouters, O.J., M. McKee, and J. Luyten, Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA, 2020. 323(9): p. 844-53.	Stated source: Wouters, O.J., M. McKee, and J. Luyten, Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA, 2020. 323(9): p. 844-53.	Stated source: Wouters, O.J., M. McKee, and J. Luyten, Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA, 2020. 323(9): p. 844-53

Paper – Authors and year	Included in Rennane et al. 2021 or Schlander et al. 2021*	Source of out-of-pocket expenses	Source of cost of capital**	Source of attrition rate
Wouters et al. 2020	Both	Phase level. SEC filings, annual 10-K and quarterly 10-Q forms). Discovery and preclinical: Costs tracked from the year a company started reporting costs. Authors assume preclinical and clinical costs incurred during initial development included in licensing fees and milestone payments.	CAPM, DiMasi, J.A., H.G. Grabowski, and R.W. Hansen, Innovation in the Pharmaceutical Industry: New Estimates of R&D costs. Journal of Health Economics, 2016. 47: p. 20-33	Phases 1–3, Wong et al. 2019 (Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2):273-286) Proportion of biologics licence applications and new drug applications approved by the FDA
Young & Surrusco 2001	Both	Phase level. DiMasi, J.A., et al., Cost of innovation in the pharmaceutical industry. Journal of Health Economics, 1991. 10(2): p. 107-42; PhRMA annual survey FDA's annual new drugs approved	Not considered	Not considered

Footnotes:

*If a paper is included in either Rennane et al. 2021 (Rennane, S., L. Baker, and A. Mulcahy, Estimating the Cost of Industry Investment in Drug Research and Development: A Review of Methods and Results. Inquiry: The Journal of Healthcare Organization, Provision, and Financing, 2021. 58: p. 00469580211059731) or Schlander et al. 2021 (Schlander, M., K. Hernandez-Villafuerte, C.-Y. Cheng, J. Mestre-Ferrandiz, and M. Baumann, How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. Pharmacoeconomics, 2021. 39(11): p. 1243-69), it will not appear in Appendix 2. Schlander et al. 2021 includes papers also reviewed by Morgan et al. (Morgan, S., et al., The Cost of Drug Development: A Systematic Review. Health Policy, 2011. 100(1): p. 4-17).

**CAPM = Capital Asset Pricing Model, a commonly used approach to estimate the COC (see Mestre-Ferrandiz et al. [Mestre-Ferrandiz, J., J. Sussex and A. Towse, The R&D Cost of a New Medicine, 2012, Office of Health Economics] for more discussion). Fama-French – a factor model for estimating the COC (see Mestre-Ferrandiz et al. [Mestre-Ferrandiz, J., J. Sussex and A. Towse, The R&D Cost of a New Medicine, 2012, Office of Health Economics] for more information).

Abbreviations: CAPM = Capital Asset Pricing Model. CMRI – Centre for Medicine Research; COC = cost of capital. FDA = US Food and Drug Administration. KMR group – company performing benchmarking, analytics and performance management. NBE = new biological entity. NCE = new chemical entity. NME = new molecular entity. PBF – Pharmaceutical Benchmarking Forum; PhRMA = the Pharmaceutical Research and Manufacturers of America; PMA – Performance Monitoring for Action; Pre-IND – pre-investigational new drug; SEC filings – Securities and Exchange Commission filings; TB = tuberculosis. Tufts CSDD = Tufts Center for the Study of Drug Development