**Supplementary Material 1:**

**Case studies to test the Re-ADAPT framework for the assessment of medicine price data sources for different scenarios**

**INTRODUCTION**

Case studies were developed to test the feasibility of the Re-ADAPT framework in assessing medicine price data sources.

For four research questions five data sources are analysed and assessed as to whether they are appropriate to inform the intended research. The data sources are fictitious but are based on real-world models.

The data sources relate to five countries that are also fictitious.

**Research questions (RQs):**

RQ1: Cross-country comparison: Analysis of the prices of 200 high-cost medicines in country D (i.e., medicines that accounted for a high share of public expenditure in a recent period of time) compared to the prices in countries A, B and C.

RQ2: Effect of the implementation of the national action plan for rare diseases in country B on the prices of orphan medicines in that country.

RQ3: Exploring the extent of discounts and other price-reducing arrangements for hospital medicines in 2-3 countries (country A should be included).

RQ4: Analysis of differences in prices between originator and generic medicines for patients in countries C and D.

**Characteristics of the analysed data sources (DSs):**

DS1: A web-based, freely available price database maintained by the Social Health Insurance (SHI) fund of country A. On the homepage it states offering price, prescription and expenditure data of medicines reimbursed by the SHI in country A.

DS2: Price lists in Excel, monthly updated (except for August), available for download on the website of the Medicine Agency of country B. There are so-called ‘lists A’ and ‘lists H’.

DS3: On the website of the national Association of Hospital Pharmacists of country B, a link to a database of hospital prices is indicated. It is a password protected, members-only database.

DS4: The Consumer Association of country D offers a web portal that states to provide price information for patients so that they can compare prices of medicines in different pharmacies. The trade name of the medicine can be typed in a search function field on the website, and the prices of the medicine in different pharmacies on that day are indicated. At that website, several studies analysing changes in medicine prices over time and differences between originator and generic medicines are published.

DS5: A data provision service of a commercial provider that announces to offer price and sales data of representative market segments for countries A, B, C, D and E. Further information, including cost estimates, will be provided at request.

**Country characteristics (national pharmaceutical pricing and reimbursement frameworks):**

Country A: Price regulation for reimbursable medicines in the outpatient sector. Social health insurance provides coverage of outpatient medicines at wholesale price level. The prices of outpatient reimbursable medicines are the same for all price types throughout the whole country due to statutory wholesale and pharmacy mark-up schemes applicable for outpatient reimbursable medicines.

Country B: Price regulation for reimbursable medicines in the outpatient and inpatient sectors. The positive list (i.e. a list that includes all medicines considered eligible for public funding) is split into two parts: category A (list A) for the outpatient sector and category H (list H) for the inpatient sector. For all price types (ex-factory, wholesale and pharmacy retail prices), the prices of outpatient reimbursable medicines are the same throughout the whole country due to statutory wholesale and pharmacy mark-up schemes applicable for outpatient reimbursable medicines. Ex-factory prices of hospital medicines are also valid for the whole country, but actual purchase prices negotiated by hospitals are anecdotally known to be lower for several medicines. No distribution mark-ups (wholesale and pharmacy) apply for the inpatient sector.

Country C: No information on the policy framework in country C available in literature.

Country D: Outpatient prescription-only medicines are subject to price regulation and are reimbursed by the public payer. There is free pricing for non-reimbursable non-prescription medicines for all price types (i.e., ex-factory, wholesale and pharmacy retail prices). The pharmacy retail prices of the same medicine are anecdotally known to differ between pharmacies in metropolitan areas.

Country E: Policy framework in country E is the same as in country A.

**How to read the table assessing the data sources?**

* The eight assessment criteria (six mandatory and two secondary criteria) of the Re-ADAPT framework are listed in the first column.
* For each criterion, first each data source (DS1 – DS5) is assessed (one cell each, same row).
* Then the appropriateness for answering each research question (RS1 – RS4) is presented summarily for all data sources (still same row, each cell now for one RQ but all DSs). In the cases of the assessment of the criteria ‘reliability and sustainability’ and ‘easy handling’, the cells relating to the RQs (same row) were merged since no differences in assessment findings were identified between the RQs.

After the table, summarizing conclusions are drawn per data source and per research question.

**Assessment of the data sources**

| **Criteria** | **Assessment** | | | | | **Conclusions** | | | |
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|  | **Data source 1** | **Data source 2** | **Data source 3** | **Data source 4** | **Data source 5** | **Research** **question** **1** | **Research** **question** **2** | **Research** **question** **3** | **Research** **question** **4** |
| **Re**liability and sustainability | Government agency as data provider, contact details available, data can be easily checked | Government agency as data provider, no contact details for requests indicated | Content and quality of the DS cannot be assessed, hospital pharmacy association is likely the data provider | Consumer association is likely the data provider, general contact details available | Content and quality of the DS cannot be assessed due to non-access-ibility, further investigation is needed | General for all DS (DS1-DS4): Reliability and sustainability of the data source are key overarching prerequisites that are relevant for any of the defined research questions.  At first glance, DS1-DS4 appear to be reliable and probably also sustainable. DS5 can also be a good option; however, it should be checked whether, or not, it is a well-established DS. The latter can be explored by asking peers about experiences and/or reviewing use of DS5 data in publications. Even if DS1-DS4 are run by government bodies or official associations, their content, quality and reliability as well as feasibility in terms of the other assessment criteria should be further explored. | | | |
| **A**ccessibility | Freely accessible | Freely accessible | Not accessible. Further investigation is needed whether the DS can be accessed and under which conditions (to be clarified whether possible access will be limited to specific data, and/or whether data from the DS will be provided but no access to the primary source. | Freely accessible but further publications suggest that the DS provider has access to more data than the ones made accessible on the website. | Data service. No access to primary price data but it is promised to supply, against payment, the requested data. | If the research budget allows purchase of data, the DS5 provider could be addressed to provide further information of characteristics of their price data (including a sample of data) of countries A, B, C and D. If they are not willing to provide a demo version for all requested countries, focus shall be put on country C, or countries C and D. In parallel, the other DSs (especially DS1, DS2 and DS4) could be explored (testing for a few medicines the freely accessible DSs and contacting DS providers for further information) to learn whether, or not, these DSs could be used to cover countries A, B and D, respectively. | DS2 appears to be a promising option to supply required data; free access to DS2 allows checking the DS feasibility for a sample of medicines. | Free access to DS1 allows checking whether, or not, this DS can provide the necessary data (in particular with regard to the criteria P – scope of pharmaceu­ticals and T – price types: are price data for the inpatient sector included?). Though not publicly accessible, DS3 appears to be promising in this respect, and DS provider should be addressed whether their DS offers the required information for country B, and whether, or not, it would be made accessible for research. Exploratory talks could also be done for DS5. | Unless any further DS could be identified for country C, DS5 would be the sole DS for supply of data in country C and, maybe also for country D. However, data might be not accessible if there is no budget for the research. If DS5 is considered for possible selection, DS providers should be addressed for further information and a sample version. Researchers might ask if they get data for free and at a discounted rate for their use in re­search. For country D, the consumer association could be asked that they have and could provide access to these price data (free accessi­bility allows checking and shows that DS4 does not provide the |

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| **A**ccessibility *(cont.)* |  |  |  |  |  | In such a case, provision of data of DS5 could be limited to one or fewer countries. As DS5 states to also offer sales data, it may also serve a possible source to identify the top 200 medicines in country D, if needed. |  |  | needed data but there are indications that the consumer association might have more data). |
| **D**ate of the data | Free access to the DS allows checking the level of information about the date(s) of the data: Next to the data it is written ‘last update’ and a date. No historical data are found. As soon as there is a change in the price, the new price appears to be indicated (no further information of the previous prices). | Monthly updates (except for 1 of 12 months). Free access to the DS allows checking the availability of retrospective data (how far in the past are data available?). | In case that access to data of this DS would be granted, the detail of information about the date(s) needs to be explored with the DS provider. | Free access to the DS allows checking the level of information about the date(s) of the data. First analyses suggest current data (possibly daily updates), but without indication of the date (and no access to retrospective data). | In case that access to this DS would be granted, the detail of information about the date(s) needs to be explored with the DS provider. | The research refers to a current (or very recent) point in time. If the date of the data can be identified and access of data be ensured, in principle, all DSs (DS1-DS5) meet this assessment criterion. | DS2 appears to be a feasible DS that allows an interrupted time series analysis at monthly basis (lack of data for one month is a minor limitation). It should be checked in advance if data are available for the whole defined observation period. | Similar assessment as for RQ1. | Similar assessment as for RQ1. |

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| Geographic scope (**a**rea) | DS for country A.  Analysis of policy framework suggests that included price data are applicable for the whole country A. | DS for country B.  Analysis of policy framework suggests that included price data (officially published list prices) are applicable for the whole country B. | DS likely for country B (since it is provided by a national stakeholder of country B). No further information is known; further details need to be explored with the DS provider. | DS for country D.  Meta information suggests coverage of different pharmacies (dispensaries), however, it is not clear whether, or not, they are representative. More information on the included pharmacies (number, geographic distribution and coverage) needs to be explored with the DS provider. | According to information provided to the public, coverage of country A, B, C, D and E. Open questions addressed for the other DSs are also applicable for this DS and require requests to the DS provider given the non-accessibility of the DS. | If compliant to other assessment criteria, DS1 and DS2 can be chosen for data retrieval in coun­tries A and B. In addition, the providers of DS5 can be asked which methodological approach they use to deal with the price data variation in country D and, in case of a similar policy framework in country C, in country C. If it meets the other assessment criteria, DS4 might prove to be another feasible source since the majority of the high-cost medicines likely fall under price regulation (no price variation) and for others, assumptions could be taken (e.g. average of the price data of a pharmacy in a metropolitan area and of a pharmacy in a rural area). | DS2 provides data valid for the whole country and appears to be the most appropriate DS. | There are price differences between hospitals in country B, and a policy framework investigation of intended further countries for the survey suggests that these differences exist in other countries as well. DS3 likely provides this information for country B. To be checked with the provider of DS5 whether, or not, DS5 could provide the needed data. | Investigation of DS4 is needed to confirm if it could provide the pharmacy retail price data for country D. For medicines with different prices across the country, development of appropriate methodological approaches is needed (e.g. selection of specific representative areas such as large cities, smaller towns, villages in rural areas and use of averages, or weighted averages, of the data). Contacts to the providers of DS5 can help get the information if their service offers data on both originator and generic medicines. |

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| Scope of **p**harmaceuti­cals | According to the meta information, the DS contains medicines reimbursed by SHI. Analysis of policy framework suggests that the DS only includes outpatient medicines (as inpatient medicines are not covered by SHI). Free access to the DS allows checking for inclusion of non-reimbursable, and inpatient medicines, if needed. | The provision of ‘list A’ and ‘list H’ suggests coverage of both outpatient and inpatient sectors, but likely limited to reimbursable medicines. Free access to the DS allows checking of coverage. | The information on the website suggests coverage of medicines used in hospitals but it is not known. It needs to be explored with the DS provider. | Likely limited to outpatient medicines. Further information (reimbursable / non-reimbursable, prescription / non-prescription medicines) needs to be requested from the DS provider. | Not known. DS provider needs to be addressed for clarification of indicated ‘market segments’. | If the price study is intended to cover both outpatient and inpatient sectors (high-cost medicines are likely, to a large extent, available in hospitals), the assessment of the DSs should investigate whether the selected DSs also provide data of medicines used in hospitals. While DS1 and DS2 likely qualify for the study to cover countries A and B, the fact that DS1 is maintained by an authority responsible for outpatient reimbur­sable medicines may suggest that DS1 only includes outpatient medici­nes. Lists H of DS2 likely include data of medicines used in hospitals but this needs to be che­cked. DS4 probably does not offer price data of medicines applied in hospitals. DS5 providers need to be contacted for information on the scope of medicines. | DS2 appears to be the most appropriate DS, since it likely includes data of both outpatient (list A) and inpatient medicines (list H). This needs to be checked, through searching for some exemplary medicines in DS2 and, if needed, contacting the DS providers. It should also be explored whether, or not, prices of non-reimbursable orphan medicines are not in included in DS2. | DS3 might provide this information for country B. To be checked with DS5 providers whether, or not, their data would be appropriate. | Contacts to the DS5 providers are needed to learn if their service offers data on both originator and generic medicines. |

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| Price **t**ypes | Free access allows checking: DS contains wholesale prices and so-called ‘institutional prices’. | Price type not clear, it is just written ‘price’ in the national language. | Not known due to limited accessibility. It may be assumed that price types relevant for the hospital sector (official hospital procurement prices; actual discounted procurement prices) are included. | So-called ‘public prices’ are indicated. | Information leaflet announces to provide information at all relevant price types, no further information is known. | The methodology has to define at which price type, or price types, prices should be compared. For high-cost medicines, price types of particular interest are the ex-factory price as well as the ‘reimburse­ment price’ in countries with ad­vanced universal health coverage (where expenses are covered, at least partially by public payers) and the pharmacy retail price in settings with full out-of-pocket pay­ments for patients. DS1 likely allows a survey for some price types: whole­sale prices are retrieved from the DS, ex-factory prices and pharmacy retail prices can be calcu­lated based on the statutory mark-up schemes. The so-called ‘institutional price’ might be the reimbursement price (to be clarified). | DS2 (and alternatively DS5) appear to be good choices for RQ2 but price types are not clear; it needs to be clarified. Given the policy framework in country B, the price type as offered in DS2 may not nece­ssarily be the one used for the research, but further price types (in line with the study protocol) can be calculated based on the mark-up calcula­tion schemes. | For this research question, DSs should provide official hospital list prices (which are the ex-factory prices in many countries) and the discounted medicine prices (which are usually not published since they are often subject to confiden­tial negotiation outcomes). DS2 is likely to provide official hospital list prices for country B and DS5 possibly (but not very likely) for countries A, B, C, D and E. DS3 suggests that it contains discounted prices (if access were granted to the researchers) but it may also only con­tain official hospital prices. Further information of the providers of the mentioned DS are required in any case. | DS4 likely provides pharmacy retail prices but this needs to be clarified, and also whether, or not, the retail prices include value-added tax and other sales taxes. If analysis is planned to be done for other price types, it would only be possible taking major assumptions. Since the price analysis likely includes non-reimbursed non-prescription medicines, other price types such as ex-factory and wholesale prices could only be calculated based on assumed or surveyed distribution mark-up since statutory wholesale and retail mark-up regulation does not apply for these medicines. |

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| Price **t**ypes *(cont.)* |  |  |  |  |  | Possible feasibility of DS2 (for country B), DS4 (for country D) as well as DS5 (for country C and also further countries) need to be further explored with the managers of the DS, to understand for which price types information is available. |  |  |  |
| Easy handling (secondary criterion) | Free access to the DS allows piloting the collection and retrieval of data (e.g. download of data sets or only single data). | Excel lists for download likely allow for good further manipulation of the data. | Not known due to non-accessibility of the DS; to be clarified with the DS provider | Free access to the DS allows piloting the collection and retrieval of data. | Not known due to non-accessibility of the DS; to be clarified with the DS provider. | *Not applicable for an assessment with regard to the research questions. In principle, the more data points to be analysed, the more important the ‘convenience’ of use and handling of data becomes.* | | | |
| Additional information (secondary criterion) | Free access to the DS allows checking which further information is provided. | Free access to the DS allows checking which further information is provided. For each medicine, its prescription status, patent status (originator / generic medicine) and whether, or not, it is an orphan medicine is indicated. | Not known due to non-accessibility of the DS; if needed, to be clarified with the DS provider | Free access to the DS allows checking. DS is based on trade names; no information on active ingredients. | Not known due to non-accessibility of the DS; if needed, to be clarified with the DS provider. | Volume information can be helpful because this would allow weighting price data to account for their relevance in the markets. DS1 (prescription data for country A) and DS5 (sales data for all countries of the analysis) appear to be able to provide this information. Additional informa­tion can also be retrieved from other DSs. | The information which medicines have been designed as orphan medicines is appreciated supportive information (otherwise, this information would have been to retrieved from other DSs). | Further information of the type of price-reducing arrangements can be helpful (e.g. retrospective arrangement, bundling). | A classification of whether a medicine is classified as originator or generic would be helpful. To be checked whether this is provided in DS5. DS4 does not provide this information, and presentation of the medicine data per active ingredient would be more helpful for an originator / generics price analysis. |

**CONCLUSIONS**

**Conclusions per data source**

**DS1** appears to be a useful DS for price data of reimbursable medicines in country A that may be used for intra-country as well as for cross-country price studies. It seems to allow access to all common price types (some listed in the data sources, others can be calculated based on the statutory mark-up regulation). However, DS1 may be limited to the outpatient sector. Furthermore, price information of outpatient non-prescription medicines is most probably not included since non-prescription medicines in country A are not reimbursed. Even if the DS is publicly accessible which allows preliminary investigation, contacts to the DS provider are strongly recommended for further clarification (e.g. on the scope of the data, frequency of updates). No time series analysis can be done based on the data included in DS1 (however, the DS provider might provide these data separately at request).

**DS2** appears to be a useful data source for price data of medicines in country B that may be used for intra-country as well as for cross-country price studies. Offering historic price data, it also allows time-series analyses. However, its scope of medicines and price types provided are not clear. There are indications that DS2 covers medicine price data of outpatient and hospital sectors (lists A and H), of the reimbursement and non-reimbursement segments as well as prescription-only and non-prescription medicines (possibly providing additional information on the reimbursement and prescription status). Though the DS is publicly accessible which allows preliminary investigation, contacts to the DS provider are strongly recommended for further clarification (particularly related to the price types included).

**DS3** appears to be promising (at least in the context of country B) since it might contain data that are usually not published (discounted hospital price data). However, since the DS is not publicly accessible, its content is not known: Does it contain actual hospital price data or official hospital list prices? In case of availability of discounted price data, which is the scope of medicines and the number and representativeness of hospitals included? Who are the primary data providers, and how often is it updated? Does it cover country B, or also further countries? In any case, these characteristics need to be clarified, and, in addition, there is the question whether, or not, and under which conditions researchers would get access to, possibly confidential, data.

**DS4** appears to be a data source targeted at consumers and patients in country D, and it may provide up-to-date information about price differences across the country. There are indications that non-prescription medicines might also be covered which could be checked for some examples. However, the content and maybe also the presentation of price information in DS4 might not be fully appropriate for research purposes. In addition, DS4 has limitations related to price types and historic data. The DS4 providers should be contacted, for clarification as well as for possible provision of further data as their publications suggest that they have further price information (e.g. historic data).

At first glance, **DS5** might be the most appealing DS for researchers since it suggests provision of data for five countries, possibly with coverage of different sectors (outpatient / inpatient, reimbursement / non-reimbursement, prescription / non-prescription segments) for assumingly all common price types. However, as the DS is not accessible, it is important to learn about the details of the DS before taking any decision. Ideally, a sample query or demo version shall be requested for further analysis. Eventually, the costs for accessing data of DS5 can provide a practical, insuperable barrier.

**Conclusions per research question**

**RQ1**: The assessment of the DSs suggests different options. If budget is available, the most convenient option appears to purchase the required data set from DS5 since it promised to cover data for all countries. However, before taking this decision, contacts with the DS provider are needed, and it has to be clarified whether the data actually meet the requirements (in particular with regard to scope and price types). An alternative could be to purchase data for countries C and D (or solely country D) from DS5 and use freely accessible data for countries A and B from DSs1 and 2. A change in methodology (e.g. other countries) is a possibility of last resort. In this case, country C might be substituted, but country D is apparently the benchmark country and has to be included in the price analysis. Possibly, further efforts to identify additional data sources for country D (e.g. addressing public authorities) could be fruitful.

**RQ2**: DS2 appears to be the most appropriate DS to deal with RQ2 since it provides retrospective, monthly data, possibly for outpatient and inpatient sectors in country B. DS2 might be focused on reimbursable medicines; in this case, the study would have the limitation to only cover the reimbursement segment (however, the majority of orphan medicines will likely be reimbursable). Free accessibility of DS2 allows checking for some medicines, but still the DS provider should be addressed for further clarification, in particular with regard to the price type included. Apart from possibly DS5 (against payment), other identified DSs cannot be used to work on RQ2.

**RQ3**: The only DS that might qualify is DS3 (however, possibly only for country B, and not for country A which would be key for this research). Nonetheless, the content of DS3 data first needs to be clarified. In addition, there is high likelihood that, if the DS contains confidential data, access will not be granted. Traditional price data collection from existing DSs is probably not a feasible approach to answer RQ3. Other survey methods, including on-site surveys in hospitals (with agreement to confidentiality clauses to data providers, for instance) should be explored.

**RQ4**: For the time being, DS5 seems to be the most appropriate DS but it has to checked whether, or not, it actually provides needed data. It could be an option to reconsider the selection of countries (e.g. including country B and also country A) since DS2 and DS1 appear to be good choices. Alternatively, use of DS4 for country D (with acknowledged limitations) and an on-site survey in country C could be another approach.