Administrative information

Title: Research Protocol – Orphan drugs - access and unmet needs in 194 countries and six regions: a comprehensive policy review with content analysis

Registration: The protocol of this study will be available online (http://www.pharma.hku.hk/sweb/CSMPR/) from the Centre for Safe Medication Practice and Research, The University of Hong Kong.

Authors: Xue Li#, Adrienne Y L Chan#, Vivien K Y Chan, Sten Olsson, Min Fan, Mark Jit, Mengchun Gong, Shuyang Zhang, Mengqin Ge, Swathi Pathadka, Claudia C Y Chung, Brian H Y Chung, Celine S L Chui, Esther W Chan, Gloria H Y Wong, Terry Y Lum, Patrick Ip*, Ian C K Wong*

Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy (X Li PhD, A Y L Chan MPH, V K Y Chan BSc, M Fan MPH, M Ge MPH, S Pathadka PharmD, C S L Chui PhD, E W Chan PhD, Prof I C K Wong PhD), **Department of Paediatrics and Adolescent Medicine** (X Li, C S L Chui, C C Y Chung MSc, B H Y Chung MD, P Ip MPH), **Li Ka Shing Faculty of Medicine, School of Public Health** (Prof M Jit), **Department of Social Work and Social Administration, Faculty of Social Sciences** (X Li, C S L Chui, G H Y Wong PhD, Prof T Y Lum PhD), **Sau Po Centre on Ageing** (G H Y Wong, Prof T Y Lum), **University of Hong Kong, Hong Kong, China; International Society of Pharmacovigilance, London, UK** (S Olsson MSc); **Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK** (Prof M Jit PhD); **Modelling and Economics Unit, National Infections Service, Public Health England, London, UK** (Prof M Jit); **National Rare Diseases Registry System of China, Beijing, China** (M Gong MD, Prof S Zhang MD); **Rare Diseases Research Center, Chinese Academy of Medical Sciences, Beijing, China** (M Gong, Prof S Zhang); **Peking Union Medical College Hospital, Beijing, China** (Prof S Zhang); **and Research Department of Policy and Practice, University College London School of Pharmacy, London, UK** (Prof I C K Wong)

# authors with equal contribution

Correspondence to:
Professor Ian CK Wong, Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China. Email: wongick@hku.hk
Dr Patrick Ip, Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China. Email: patrickip@hku.hk

Contributors: XL, ICW, and AYC conceived of and designed the work. AYC, SO, VKC, and XL collected data from government sources. AYC, MG, and XL screened and selected academic literatures. AYC screened and selected governmental documents. AYC extracted and analysed information from all selected publications. VKC crosschecked the results. FM and SP carried out data visualisation and statistical analysis. AYC wrote the first draft with support from VKC and XL. All authors interpreted results and critically revised the manuscript. XL, PI and ICW supervised the study. All authors approved the final version of the manuscript.

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INTRODUCTION

Rationale

"Orphaned" due to low prevalence and barely recoverable costs, rare disease patients were deprived of equal chances to treatment. The collective burden of rare diseases was significant, and could be addressed through policies that optimise research and development, licensing, pricing, and reimbursement of orphan drugs. Several literatures reviewed country-specific orphan drug and rare disease policies but were limited by the scope of selected countries, or were restricted to English peer-reviewed journal articles.[1-3] As such, current development of orphan drug policies on a global scale remained unclear. We aimed to aggregate existing orphan drug policy frameworks to inform policy formulation globally.

Objectives

This study aims to provide an up-to-date global overview of orphan drug policies. The following objectives are set:

1. To summarise and visualise the presence of orphan drug policies by country;
2. To summarise orphan drug policies by content themes through extracting and analysing texts from governmental documents and academic literature;
3. To visualise orphan drug policy coverage by content themes.

METHODS

Information sources

Publications issued by governmental authorities will be obtained through a standardised *Google* search, websites of drug regulatory authorities (DRAs) of each country, and direct emails to DRAs. Emails will be sent to national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring by the author SO, assisted by the programme coordinating office at WHO-HQ, Geneva, the network of the International Society of Pharmacovigilance (ISOP). Academic literature articles will be retrieved from academic databases. The databases searched included: PubMed, EMBASE, Web of Science, and the Cochrane Library.

Search strategy

The literature search is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search will be conducted since 1st November, 2018, and will be last updated on July 31, 2019.

A search strategy was developed with regards to two components: orphan drugs and policies. Keywords included, [("Orphan" or "High Cost" or "Rare Diseases") and ("Drugs" or "Medicines" or "Pharmaceuticals") and ("Legislation" or "Regulation" or "Policy").

The thesaurus vocabulary of each database is used alongside combinations of various search terms relevant to the keywords to optimise the sensitivity and specificity of our search. An additional manual reference search will be conducted from the initial articles retrieved.

Google search strategy

A Google search was performed using combinations of the terms.
"orphan drug"/ "rare diseases" + [country name] in the official language of the respective countries/regions using Google translate.

Academic search strategy

PubMed (Search date: 1st November, 2018; updated on 31st July, 2019)

(((((((orphan[Title/Abstract] OR high cost*[Title/Abstract] OR rare disease[Title/Abstract])))) AND ((drug$[Title/Abstract] OR medicine$[Title/Abstract] OR pharmaceutical$[Title/Abstract])))))

AND
((legislation$ or regulation$ or policies))))

NOT
("child, orphaned"[MeSH Terms] OR ("child"[All Fields] AND "orphaned"[All Fields]) OR "orphaned child"[All Fields])

EMBASE via Ovid (Search date: 1st November, 2018; updated on 31st July, 2019))

((orphan or high cost* or rare disease).ab,ti.) and ((drug$ or medicine$ or pharmaceutical$).ab,ti.)

and

((legislation$ or regulation$ or policies).af.)

Cochrane Database of Systematic Reviews Issue 10 of 12, October 2018 (1st November, 2018; updated on 31st July, 2019)

(legislation$ or regulation$ or policy$)

AND

((orphan or rare or high cost) and (drug$ or medicine$ or pharmaceutical$)):ti,ab,kw
(Word variations have been searched)

Web of Science Core Collection 1956-2018 (1st November, 2018; updated on 31st July, 2019)

(TS= (((orphan) or (high cost*) or (rare disease*)) and (drug$ or medicine$ or pharmaceutical$)))

AND

(TS= (legislation$ or regulation$ or policies))

Data management

Citations of retrieved articles from electronic databases will be imported to Endnote X9 where the records will be stored and managed. Records not retrieved from the electronic databases such as legal documents extracted from government websites will be managed manually by an excel spreadsheet.

Eligibility criteria and selection process

All publications (from governmental and academic sources) that described any policies, legislation, or regulation related to issues about orphan medicine and drugs developed to diagnose, prevent, or treat rare diseases will be screened. These issues include, but not limited to patient access, drug availability, marketing authorisation, licensing, pricing, reimbursement, and more.

Government documents that specified any orphan drug policies will be included. Policies implemented by non-governmental entities will not be considered. For academic literature articles, titles and abstracts of all retrieved articles will be reviewed for relevance in consideration of the inclusion and exclusion criteria. Screening results will be further crosschecked. Selected articles will be read in full. Only peer-reviewed policy research (study designs included: review with methodology, comparative analysis, policy analysis, mixed methods) are included in this review. Literature without a method section such as commentaries, editorials, narrative reviews are excluded. However, when identified from manual reference list search of included studies, excluded literature will be added back to the included studies due to the its strength of evidence being validated through robust methodology.

Data collection process and data items

A data extraction form will be developed and administered.

To assess the availability of evidence, we extracted information namely, country name, region name with reference to WHO regional classifications, the establishment status of DRA, the name of the DRA, the status of the DRA website, presence of drug regulation documents, presence of orphan drug policy in the drug regulation document.

For any identified publications containing orphan drugs policy, the following items will be extracted: title, article number, publication year, localised terms, authority involved, direct texts from the document.

Content of the drug regulation document related to orphan drugs will be extracted, the content texts will first be input on an excel spreadsheet based on pre-identified themes used in previous reviews.[1-3] Content texts that cannot be categorised will generate a new theme to the extraction table. Additional themes are further identified during data extraction with assigned codes until exhaustion of themes and sub-themes identification. A consensus meeting will be held to group different themes into various domains. *Google translate* will be used to interpret the results from countries in non-English.

National Orphan Drug Policy	Legislation, Orphan Drug Designation, Definition of rare disease, National Rare Disease Plans, Cross-border Regulation
Access to treatment	Orphan Drug Marketing Authorization, Accelerated Procedures
Incentives	Financial Incentives, Non-Financial Incentives
Marketing Exclusivity	Monopolisation
Pricing	Free vs Fixed Pricing
Reimbursement	Health Technology Assessment, Co-Payments, Post marketing surveillance, Managed Entry Agreements
Program or Strategy	Diagnosis programs, Patient engagement, Research, Coordination of care

Table 1. Pre-identified themes and sub-themes from previous reviews for content analysis

Data synthesis and visualisation

After the consensus meeting, the extracted information will be summarised. References to the documents will be made, such that interested parties may refer to the citations for further information. The summarised information will be crosschecked. Consensus meetings will be held regularly until absolute agreement of the results are reached.

Orphan drug policy establishment in each country/area will be visualised geographically in a global map. The annual proportion of countries/areas with established orphan drug policy among number of countries/areas with the same World Bank defined income levels will be plotted as a line graph. Orphan drug policy scope in each country will be visualised in the form of a heat map. Each theme in each country/region will be represented by a percentage of number of sub-themes addressed in the policy documents over the number of sub-themes identified globally.

The statistical difference of incomes (gross national income per capita) between countries/areas with and without established orphan drug policy will be tested by the Mann-Whitney U Test. The normality of variables will be checked by density plot, Q-Q plot, and Shapiro-Wilk's method. The linear relationship between country incomes and the number of themes covered by orphan drug policies will be analysed by Spearman Correlation. All analysis will be conducted by R statistical software (version 3.6.0). Package ggplot2 will be used for visualisation.

ETHICS APPROVAL

This is a systematic review based on research database and google search with patient privacy data involved and no patient contact. Ethics approval is not required.

REFERENCES

1. Gammie T, Lu CY, Babar ZU. Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries. PLoS One. 2015;10(10):e0140002.
2. Khosla N, Valdez R. A compilation of national plans, policies and government actions for rare diseases in 23 countries. Intractable Rare Dis Res. 2018;7(4):213-22.
3. Dharssi S, Wong-Rieger D, Harold M, Terry S. Review of 11 national policies for rare diseases in the context of key patient needs. Orphanet J Rare Dis. 2017;12(1):63.