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Manuscript title

RWE in healthcare decision making: Global trends and case studies from Latin America

Running title

RWE in healthcare: focus on Latin America

Précis

The sources, characteristics and uses of Real World Evidence in healthcare are reported with case studies, literature and database reviews in four Latin American countries.

Total number of each

1) Text Pages: 19
2) Tables: Two plus three in the appendixes presented as supplementary materials
3) Figures: One

Word count

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Abstract

Objectives: Real-world evidence (RWE) is increasingly used to inform health technology assessments (HTAs) for resource allocation, which are valuable tools for emerging economies such as in America. However, the characteristics and uses in South America are unknown. This study aims to identify sources, characteristics and uses of RWE in Argentina, Brazil, Colombia and Chile, and evaluate the context-specific challenges. The implications for future regulation and responsible management of RWE in the region are also considered.

Methods: A systematic literature review, database mapping, and targeted grey literature search were conducted to identify the sources and characteristics of RWE. Findings were validated by key opinion leaders attending workshops in four South American countries.

Results: A database mapping exercise revealed 407 unique databases. Geographic scope, database type, population and outcomes captured were reported. Characteristics of National Health Information Systems show efforts to collect interoperable data from service providers, insurers and government agencies, but that initiatives are hampered by fragmentation, lack of stewardship and resources. RWE is mainly used in South America for pharmacovigilance and as pure academic research, but less so for HTA decision-making or pricing negotiations and not at all to inform early access schemes.

Conclusions: The quality of data collected in real-world in the case-study countries varies and RWE is not consistently used in healthcare decision-making. Authors recommend that future studies monitor the impact of digitalisation, and the potential effects of access to RWE on the quality of patient care.

Highlights

Through collecting case studies from four South-American countries, this study found that the collection and uses of Real World Evidence (RWE) in healthcare decision making is inconsistent across regions, providers and insurance schemes. RWE initiatives are somewhat hampered by fragmentation, lack of stewardship and limited resources.

A literature review and database mapping revealed that RWE is mainly used in South America for pharmacovigilance and academic research, less so for HTA decision-making or pricing negotiations, and not at all to inform early access schemes.

1. Introduction

Healthcare decision-makers, the pharmaceutical industry, patients and clinicians are increasingly using "real-world" data to assess the safety, effectiveness and costs of interventions [1,2]. Real-world data (RWD) refers to health care delivery data that is routinely collected from sources such as providers' paper or electronic health records (EHRs), billing data, clinical registries, surveys and surveillance data from health care activity [2]. Real world evidence (RWE) is derived from the analysis of RWD and refers to the clinical evidence of a medical product's benefits and risks, safety and effectiveness [2]. It is used globally to complement data from randomized controlled trials (RCTs), for example when assessing the cost-effectiveness and safety of interventions in clinical practice, enabling the generalization of clinical findings to a more inclusive and larger population [1].

It has long been recognised that evidence from RCTs is insufficient when used as the sole basis for coverage or decision-making in healthcare [1,3]. While clinical efficacy can be demonstrated using RCTs, required length of trials, the exclusion of major population subgroups and its costs renders them controversial as the only basis of evidence for health technology assessments (HTAs) [1,4]. To complement RCT data, regulators such as the Food and Drug Administration (FDA) in the United States (US) and the European Medicines Agency (EMA) have been gradually incorporating the use of RWE to assess the value of new interventions and monitor their safety and effectiveness following approval for clinical use [2,5-7]. This is often a condition to early authorisation or fast-track approval of treatments that fulfil major unmet medical needs, key public health issues or, rare diseases [8]. The healthcare sector is increasingly willing to accept less certainty in treatment effectiveness in return for fast patient access to innovative treatments [8,9]. In return for initial licensing for a specific patient population based on limited clinical data, research institutions and pharmaceutical companies are becoming more advanced in mining data to monitor and evaluate the safety and

effectiveness of their interventions to reduce uncertainty in the post-marketing authorization phase [9].

In contrast, emerging economies rarely capture transferrable and reliable RWE that can be used by regulators or for HTA decision-making. Regions such as Latin America, Asia Pacific and Africa tend to have significant unmet medical needs, major public health issues and populations with a high burden of communicable and chronic diseases. This might lead to potential health outcome benefits and cost-savings derived from the introduction of RWE to inform resource allocation and fast-tracked regulatory and coverage decisions.

The healthcare sector in Latin America is transforming. In recent years, the region has recorded an increase in healthcare spending [10], expanded health coverage and launched several successful public health initiatives across the region [11]. While there is an increasing aging population and the region is experiencing an epidemiological shift from infectious to chronic diseases, health outcomes and life expectancies are improving dramatically [12,13]. HTA agencies and regulations have emerged across the Latin American countries to contain the increasing costs of public healthcare by improving the allocation of limited resources. However, reliable and robust sources for RWE are few, so local decision makers are reluctant to tolerate the risk of selection bias, uncontrolled confounding and endogeneity derived from unreliable RWD. Furthermore, if their internal capabilities to apply highly sophisticated analytical methods are limited, RWE is even less valued. Thus HTA evaluations continue to rely solely on data from RCTs conducted abroad as the basis for decision-making. While some reimbursement schemes for high-cost treatments require applications supported by RWE, it has not yet been harnessed and applied by either public- or private-sector stakeholders to its full potential.

Despite these limitations, Latin America has recently seen a surge of interest in RWE, with increasing numbers of academics and pharmaceutical companies seeking access to or creating

databases and registries to inform HTA submissions and best practices in the healthcare sector[11]. This study presents the sources and uses of RWE in four South-American countries; Argentina, Brazil, Chile, and Colombia, with an evaluation of the context-specific challenges of data generation and limitations of healthcare system infrastructure. Finally, this study considers the implications of this research for future regulation and responsible management of RWE in South America.

2. Methods

We performed a systematic literature review, a database mapping, and a targeted search in the grey literature and the websites of governments and relevant public agencies. In addition, we developed a series of RWE workshops in Argentina, Brazil, Chile and Colombia where we consulted key opinion leaders (KOLs) and validated information previously collected through the review. These half-day workshops included three presentations, each followed by a discussion session, and were attended by a variety of local stakeholders including representatives of the Ministries/Secretaries of Health, public/private HMOs, physicians engaged in outcomes research, Statistics Departments, etc. Additional information on the workshops can be found in the Supplemental Materials.

A systematic search was run in the LILACS, MEDLINE and CAB Global Health databases to identify sources of RWD and assess the availability and characteristics of RWE in Latin America. The search strings included the following terms: 'observational' or 'non-interventional' or 'retrospective' or 'cohort' or 'survey' or 'cross sectional' or 'dataset' or 'real world' data in Latin America and the four case study countries (see full search string in appendix 1). The articles were screened for relevance and they were excluded if the target population did not include Argentinian, Brazilian, Chilean and/or Colombian patients; if the outcomes were not health-related; and if the study design was a clinical trial, literature review,

feasibility analysis or meta-analysis. Reason for exclusion was recorded and, for those included, basic information pertaining to the data source used was extracted (name, geographic coverage, indication and type of data). The identified sources of RWD were de-duplicated, and categorised into following three database types: i) administrative databases, ii) clinical and patient registries, and iii) national health information systems including surveillance.

KOLs were consulted on the generation and uses of RWE in their respective countries, to validate the findings of the literature search, to identify the challenges of incorporating RWE into healthcare decision making, and finally to ascertain areas of opportunities. To supplement KOL contributions, a targeted literature review was conducted with a focus on health policy in Argentina, Brazil, Colombia and Chile. Grey literature, peer-reviewed articles and online sources were reviewed from societal, clinical and industry perspective. Search terms for this part of the investigation were the following: 'real-world data', 'real-world evidence', 'early-access programs', 'health technology assessments', 'health economic evaluations', 'expanded access programs', 'performance-based risk-sharing agreements', 'compassionate use programs', 'managed-entry agreements', 'conditional reimbursement agreements', 'coverage with evidence development', and 'pharmacovigilance'. The authors scanned and categorized the contents into three main findings alongside KOL contributions: i) the generation of RWE from secondary sources: administrative, registry/clinical and national health information systems, ii) the uses of RWE for pharmacovigilance, the monitoring of safety and drug utilization, as well as HTA assessments, and iii) the methodological challenges of using RWE in practice.

3. *Results*

3.1. **Sources of RWD in Latin America**

Figure 1 presents the PRISMA diagram for the systematic literature review (see Appendix 2 for additional information). Searches of the LILACS, Medline and CAB global health databases retrieved 681 potentially relevant publications from the case-study countries, Argentina, Brazil, Chile and Colombia; of which 11 were removed due to duplication. Of the remaining 670 studies, 487 were found to be based on relevant sources of RWD. The remaining 212 studies were excluded based on study design (n=71), geographic coverage (n=135), non-health related outcomes (n=6).

In the 487 articles screened for abstraction, 407 unique data sources were identified after identifying multiple data sources within articles, and de-duplicating databases (n=80). It was found that most databases had a population coverage of one hospital or county (n=201), and that fewer studies cited data sources with national (n=105) or regional (n=75) coverage. The least common were international databases (n=24). Databases were categorised into types, with clinical databases (including EMRs) or patient registry databases being the most common (n=190), health information systems, including surveillance systems, being the second most common (n=101) and finally administrative databases being the scarcest (n=66).

Most unique databases that were identified in the search covered the Brazilian population (n=240), followed by Chile (n=62), Colombia (n=46), Argentina (n=44) and general Latin American databases (n=15). The most common studied outcomes were hospital-related infections and treatment-related adverse events (pharmacovigilance) (13%), followed by cardiovascular diseases (11%), oncology (11%), hospitalizations, surgery and emergency care data (8%), maternal and new-born health (7%), TB & other respiratory diseases (5%), and STDs including HIV/AIDS (4%).

Input from KOLs and targeted literature searches informed definitions of database types as follows; administrative databases are classified as data repositories managed at a regional or organisational level to capture process indicators from reimbursement, facility or insurance data [3]. They are used to assess the economic impact of treatments using cost data [11]. Secondly, health information systems (HIS) are public health surveillance systems characterised by the ongoing and systematic monitoring of health events to reduce morbidity and mortality [14]. They typically monitor key health indicators such as disease prevalence, burden and services utilization. Outputs can be used to inform national and provincial ministries of health (MoHs) on the needs of healthcare services, and the resulting health statistics are disseminated for public access on an aggregated level. Finally, clinical and patient registries consist of observational cohort studies for a disease or treatment group, and are typically used for understanding the natural history of diseases or monitoring the associated care quality, provider performance or cost-effectiveness [3]. **Error! Reference source not found.** shows the distribution and types of RWE available in the four South-American case studies, and **Error! Reference source not found.** presents detailed information on four examples per country. For example, promising initiatives to create inter-operational national health information systems, a selection of condition-specific clinical databases, EMR systems, and finally an example of maternal and neonatal databases that typically combine administrative and clinical data, though with limited depth.

3.2. **Uses of RWE**

During the desk research phase, we identified four major uses of RWE globally; i) regulatory processes such as marketing authorization, early access schemes and pharmacovigilance, ii) HTA decision-making, iii) academic research and iv) healthcare management and financing.

Error! Reference source not found. shows the current use of RWE in South America, or lack thereof, following this taxonomy. We found that, in the countries under study, regulators

mainly use RWE for pharmacovigilance purposes. Pharmacovigilance and technovigilance of pharmaceutical products and devices are informed by real-world surveillance of adverse events (AEs) and treatment patterns. The case studies demonstrate variation between countries' pharmacovigilance regulations that apply, with Argentina's National Drug Food, and Medical Technology Administration (ANMAT) legislation requiring "corrective procedures" and Chile's ANAMED interest in building "safety profiles" using RWE for authorized drugs.

However, there is limited use of early access schemes for treatments that meet unmet needs or to obtain historical comparators for the assessment of orphan indications. While pharmaceutical producers in the European Union and United States can apply for early access, through Adaptive Pathways (EU) or Breakthrough Therapy (US) designation by agreeing to collect post-authorisation RWE in exchange for early authorization of a treatment, this strategy is not used in South America where phase III RCTs are deemed to be the gold standard for marketing authorization. A rare exception is the occasional approval of Compassionate Use Programs, though no RWD collected for secondary use.

While RCTs are considered the gold standard for HTA submissions, there is a growing recognition that observational data is a key tool for budget impact analyses and economic evaluations in all South American countries (see **Error! Reference source not found.**). Across South America, payers and producers of biopharma and medical devices are using economic and effectiveness RWE to support price and coverage negotiations. However, these are the exception and are typically implemented in small populations, by the private sector and hardly ever outcomes-based. In Brazil, for instance, while access to RWE is limited by a lack of interoperability between regional and organisational systems, there is high utilization of RWE amongst HTA agencies. For example, RWE -domestic or international- was included in 88.2% of HTA submissions between 2011-2014 [15]. Elsewhere in Argentina, Colombia and

Chile, economic evaluations and cost-minimisation analyses are being conducted to support coverage decisions. However, the use of RWE in South America tends to be part of the value argumentation of pharmaceutical products, and they are not generally part of the binding market access agreements between healthcare payers and pharmaceutical producers.

Academic institutions in South America use RWE to address transferability to wider populations in the region. These, in turn, are used in economic model adaptations for HTA submissions. Academic institutions also conduct epidemiological research on mortality, incidence and prevalence of diseases based on national surveillance data to inform healthcare management and innovation. Institutions across South America are responsible for the national or regional disease-specific registries that were started as an individual initiative for self-contained research projects. Academic and governmental partnerships have also been set up to monitor the performance of the national healthcare system, improve health outcomes and monitor out of pocket expenses. For instance, Chile's MoH has begun to digitalise databases, synchronise systems collect routine population data. Also, Argentina's Plan Nacer is a government-funded auditing programme to monitor quality and allocation of resources in clinics treating uninsured women and children. In exchange for funding, clinics across Argentina contribute to a surveillance network for maternal and new-born health outcomes.

3.3. **Challenges and opportunities in the collection and consolidation of RWE**

The identification of challenges and opportunities are based on KOL inputs, the proceedings of the discussions during the workshops, and insights from the literature pertaining to the limitations of the studies reviewed. While they are multiple and diverse, there are some common challenges to overcome: as summarized below:

- Problems with the data. There is a wide variety of available data across all South-American countries. However, countries face the key challenges of data integrity, quality

and security. National variations in data collection, and patient concerns in sharing data pose a serious challenge to gathering meaningful insights from data.

- Gaps in expertise. The KOLs from Brazil, Chile and Colombia pointed out that the number of skilled personnel is insufficient to analyse the large volume of data that has, and will, become available. To benefit from RWE, all interested parties must address this gap and engage in training and capacity building.
- Lack of confidence in observational research. To capture reliable and transferrable RWE for policymaking and HTA decisions, observational research must follow good practices as highlighted in the ISPOR Special Task Force report on Real-World Evidence in Health Care Decision Making. Studies should be fully transparent, and take steps to resolve validity issues of confounding, measurement error, selection bias and missing data [16]. The aforementioned gaps in expertise and problems with the data foster a conservative attitude from the decision makers towards RWE.
- Trust Issues between users and data holders and among the latter themselves: There is a limited, not-always transparent and complex collaboration of various parties (industry, academia, hospitals, government, and payers). Data security issues and limited access affects the opportunities to analyse the data and utilize the knowledge. In turn, this reinforces another difficulty regarding the longitudinal follow-up of patient pathways through the different healthcare services. We have not identified any data aggregation platforms in the region, which speaks about the impaired cooperation.

Academics and pharmaceutical industry have advocated for an increased use of RWE encouraging other potential users to generate the data and use results. In our case studies, we identified some common opportunities to improve the use of RWE:

- The region has witnessed an extension of healthcare coverage in at least two dimensions (bigger population and more diseases/interventions covered) which exerts pressure on

healthcare budgets. Thus, there is agreement on the need to monitor results closely, particularly those pertaining to high-cost interventions.

- Data registration is improving in all the countries, with a variety of strategies to address specific issues. We have identified initiatives to extend the use of EMRs and improve registration (e.g. harmonize coding systems and languages, minimize the use of free text, train personnel on coding systems, etc.) and to improve the traceability of patients and allow for longitudinal follow-up (e.g. systems integration and central authorities aiming at extending data consolidation).
- There is a rapidly growing number, and maturing of, HTA units in the MoH and independent HTA agencies in the region.
- There is an increase in the various types of HTA institutions and units in South-America, and an increasing adoption of pharma-economic guidelines as well as evidence-based healthcare policy design, representing a promising prospect for the extended use of RWE in the region.

4. Conclusion and Discussion

The literature review indicates that, some patient-level data resources exist in the four countries under study. However, the quality of registries and databases vary and are generally locally managed without standardized coding and practices between disease groups, hospitals and regions.

The expert contributions reveal that there is occasional use of RWE in HTA submissions, and expertise to analyse the supporting data, but at the time of writing RWE is not consistently communicated to HTA agencies at a national level. Local HTA agencies leverage RWE in their decision-making process in the design of clinical practice guidelines, in systematic

reviews of efficacy and safety, as inputs in models (both economic and epidemiological) and for resource allocation. The preference for local or international RWE depends on the parameter required to be estimated. If the parameter is likely to be influenced by local practices, such as resource use or an effectiveness estimate, as opposed to an efficacy endpoint, local RWE would be preferred. If the parameter is less likely to be influenced by local practices such as the incidence of a rare adverse event, or durability of treatment response, evidence from a good quality international source may be admissible, or even preferred. HTAs need to balance the need to foster local RWE without overly delaying the assessments, which are expedited if international RWE is also considered, after addressing transferability issues.

Opportunities lie in increased capacities for regulation and pharmacovigilance in the form of mandatory post-authorisation studies or context-specific RWE guidelines. It is also consistently suggested that higher levels of patient involvement may trigger increased levels of safety and effectiveness monitoring.

This research indicates that there are four key policy implications to generating RWE and using it to inform decision making; (i) A central authority is required to steward health information systems to ensure interoperability and quality guidelines, (ii) Legal and standard practice frameworks are also needed for data anonymization and linkage that protect patient rights to confidentiality. The FDA does this by sharing only aggregated data beyond local networks, but Colombian regulators, for instance, have not put such a barrier in place, which raises privacy issues. (iii) Regulation is also required to monitor the transparency and reproducibility of results to ensure viable and mutually beneficial models for collaboration. (iv) Finally, the allocation of IT resources, training, electronic databases, and storage facilities is needed for public healthcare facilities to ensure transferability of routine data collection and patient traceability through the entire continuum of healthcare provision.

There are limitations to this study, as follows. Country-specific expert opinion was sought for each case study, resulting in some inconsistencies in the focus and depth of topics evaluated in the countries. Also, since the time of writing (June 2017 - January 2018), there may have been updates and changes in the use, laws or regulations of RWD and evidence. Finally, the pitfalls of comparing South-American health care systems within the region and to European and American health care systems should be highlighted. While no direct country-comparison is possible, the funding mechanisms, epidemiological profile and basic structure of South-American health systems are often fundamentally different to the single-payer systems in Europe or the largely private health insurance-reliant US system. In the region under study, most countries have a mix of private health care, social security financing and public provision for the poor. This means that healthcare is characterised by fragmentation, uneven coverage and the associated equity issues. Thus, these comparisons should be interpreted with care.

Recommendations for future research are first to monitor and evaluate the uses of RWE produced by the four digital initiatives investigated, SISA (Argentina), DATASUS (Brazil), SIPRO (Colombia) and Sidra (Chile). The outcomes of digitalization can be shared with healthcare systems in emerging economies in both Latin America and elsewhere, and it is recommended that a regional repository of databases to signpost users to freely available data is set up to facilitate this. Secondly, it is suggested that future research monitors the uses of RWE in HTA decisions, to pinpoint the regulatory bodies, indications and populations that include RWE in HTA submissions. Thirdly, the quality of RWD, data analyses and the resulting RWE is largely unknown. Future research should examine the transferability, reliability and regional variation in routinely collected healthcare databases, and the quality of the RWE produced. Finally, future research should to monitor the impact of systematically collecting RWD in healthcare settings on the patient experience and health outcomes. The

results of this study show that a feedback mechanism, such as Argentina's Plan Nacer, can dramatically improve patient care by financing well-run clinics that report high quality RWD.

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6. *Tables and Figures*

Figure 1: Database mapping flow diagram, adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). [14]

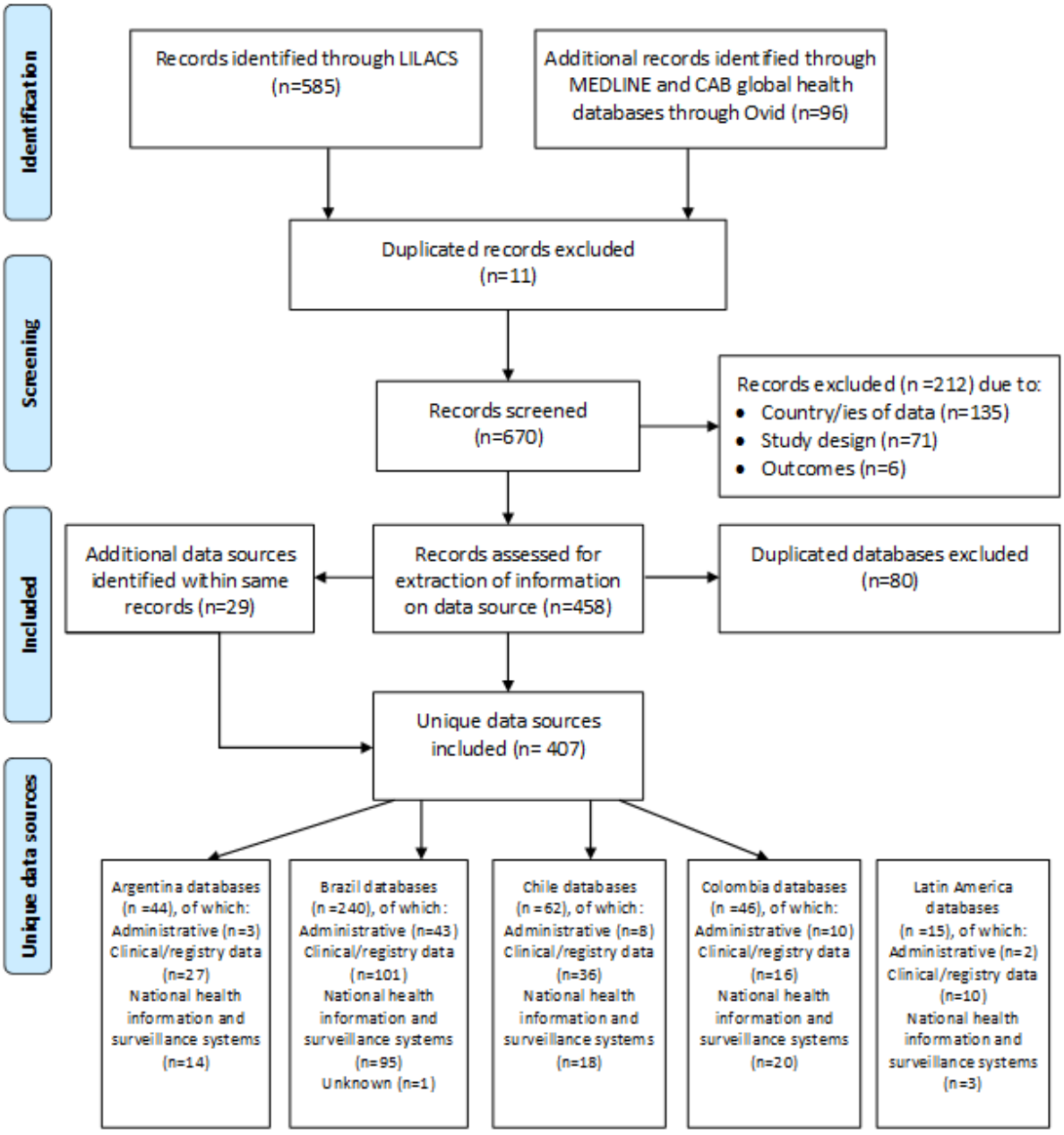

Table 1: Summary of health information systems and national health data in four Latin American countries

National Health Information Systems				
	Argentina - SISA	**Brazil – DATASUS**	**Colombia - SISPRO**	**Chile - SIDRA**
Objectives	• To improve patient care and health system decision-making amongst all stakeholders. • Optimize information management, using a single national health information system [17].	• To control payments to public and private service providers for the SUS[1]. • Collect, process, and disseminate healthcare and demographic data.	• Informed decision making, policy support, regulatory monitoring and service management [18].	• To create a national repository of health information and common EMRs
Summary	• Quick and reliable sharing of information to control validation, integrity, security and availability. • Link human resources and streamline services through an integrated database and a decentralized management system. • Argentina's national health surveillance system, mortality statistics and national hospital discharge records used to monitor history of diseases and for health policy planning such as assessing the economic impact of immunization strategies [19,20]	• Data includes indicators, services and products consumed as well as estimates of mortality and morbidity across specific populations. • Developed more than 200 information systems to better inform the MoH, plus state and municipal secretaries of health. • Examples of the uses of DATASUS are to access ICD codes, utilization of burns facilities, and the risk factors for TB in remote regions [21,22]	• Data includes patient characteristics, health insurance coverage (contributed or subsidized), health care facility main diagnosis, intervention, length of stay and condition when discharged. • Colombian MoHs and Social Protection register consolidates data from the healthcare services using ICD-10 codes [23] • Covers the population that use services within Social Security Health System [24] • Data is subject to continuous quality control testing • SISPRO has been used to analyse health care access and causes of death, as well as to monitor the rates of domestic violence and drug interactions [25-27].	• An integrated information system that connects primary with the secondary and hospital level care • Provides longitudinal data about care supplied in the health system, but also about patient outcomes. • SIDRA project aims to report on the living conditions of immigrants, diseases-specific hospital resource use and incidence rates of different diseases [28-30]. • The hospital discharge database is a country-wide hospitalizations census. • Utilization of services in the public (REM) and private sector (REMSAS) are available from the Department of

[1] The Unified Healthcare System; Sistema Único de Saúde - SUS

				Statistics in the MoH [31]
Data use by third party	• Free public access • Access with required registration (multiple levels of data access/management) [17]	• Free access to information using National Health Cards. • Restricted access to personal health records (using a card and password). Physicians can access examination results, medical procedures and medicines purchased [32].	• SISPRO offers patient-level nationwide data that is used across the LatAm region. Access is free of charge following registration process and online training for the different modules with information on affiliation, diagnosis, hospital services and medicines among others types of data. [24]	• EHRs to be accessible to all Chilean healthcare providers [33]
Limitations/Challenges	• Not yet fully implemented, still in the planning phase • Managing the various health system resources, interests and capacities • Surviving management/political changes – key factor for long-term projects • Prioritising overall benefit rather than particular interests [17]	• Longitudinal follow-up of individual patients hampered by the need to use of probabilistic matching in the absence of a unique identifier • Cannot be used to characterize the healthcare system as a whole • Limited by incompatible data and lack of common definitions of healthcare indicators • Lack of incentives for routine data collection, some patient encounters are missed and data quality varies	• The accuracy of diagnoses has been questioned. • Data tends to be of higher quality for high-cost diseases (or procedures) as data collection depends on reimbursements [34]. • Overlapping or lack of integration of different data sources collecting similar or complementary information i.e. Registries from the National Cancer Institute, the National Health Institute (INS), "Cuenta de Alto Costo", etc.	• Lack resources to unify national information systems • Compatibility issues from local health systems operating own information systems pre-SIDRA. • Synchronising records, processes and information systems is a challenge. • Supplying resources to cover transaction costs associated with system migrations is a challenge.
Disease and condition specific-clinical registries				
	Argentina	**Brazil**	**Colombia**	**Chile**
	• Immunization registry • Blood donor registry • Cancer drug bank registry • National school health registry • Chronic kidney registry Cardiovascular registry • Hearing aid care registry • HIV-AIDS patient management system [17] • National stroke registry	• HIPERDIA: hypertension and diabetes - ensures that demographic, epidemiological, morbidity and mortality data on patients are accessible • Stroke prevention in Atrial Fibrillation therapy monitor • National health and wellness survey • Kidney transplant registry, Sao	• Vaccine preventable disease registry • Vector transmitted registry • Sexually transmitted (incl. HIV-AIDS) registry • Accident registry • Intoxication registry • Chronic disease registry. • Organ transplant registry [37] • Tuberculosis surveillance database [38] • Surveillance system for domestic	• Immunization registry • Blood donor registry • Cancer drug bank registry • National school health registry • Chronic kidney registry • Cardiovascular registry • Hearing aid care registry • HIV-AIDS patient management system [17] • National stroke registry

	(ReNACer) [35]	Paulo [36]	violence (SIVIF) [27] • "Cuenta de Alto Costo" has long term information and follow up for Renal disease, HIV, and Cancer	(ReNACer) [35]
Electronic Medical Records (EMR) systems				
	Argentina - Hospital Italiano de Buenos Aires	**Brazil - Health National Cards**	**Colombia –SaludTotal and Sura**	**Chile - Mas Salud Occidente**
Summary	• Private sector hospital with exemplary health information system • Sophisticated coding system for hospitalizations and prescriptions • Facilitates cohort studies [39]	• In 2011, the MoH launched a strategy to register all Brazilians to either a public or private healthcare system [40] • The SUS national health card is used to register all citizens' diagnoses, prescriptions, and hospitalization history.	• EMRs exist but they are not integrated, as they have been developed and adopted by different HMOs and health care institutions. • Large hospitals host clinical and cost EMR systems for admitted patients, but lack some administrative data • Health insurers (such as Salud Total and Sura) have implemented EMR systems that record administrative outcomes. • EMRs rarely combine outcomes. • There is a project to unify EMR systems for different stakeholders of the healthcare system (Historia Clínica Electrónica Unificada -HCEU)	• Among many objectives, Mas Salud Occidente aims to manage the patient interaction with the healthcare network (for e.g. waiting lists and referrals) • Manages resources such as medical supplies and availability of beds [33,41]
Limitations/Challenges	• The sample population at Hospital Italiano may not be widely representative of the Argentinian population because it is a private hospital.	• A 2017 study revealed that in a sampled population, only 50% were registered and errors including incorrect demographic data [42]	• Lack of IT infrastructure and connectivity limits integration of the data available from Colombia's healthcare system	• Lack of training and incentives for healthcare professionals to maintain pharmacovigilance systems
Example of national condition-specific database for surveillance and informing health policy: Maternal and Neonatal databases				
	Argentina - Plan Nacer	**Brazil - SisPreNatal**	**Colombia - ICBF**	**Chile - FONSA & MoH databases**
Summary	• Funding and auditing programme to monitor quality and allocation of resources in clinics treating uninsured women and children. • WB and MoH financially incentivise healthcare providers.	• Software developed by DATASUS for collecting follow-up data on more than 3 million pregnant women in 5,000 municipalities in the Unified Health System [32].	• Data freely accessible on the users and resource use of childhood health promotion and disease prevention services, covering early childhood nutrition and programs for families and communities. [51].	• National Observatory of the rights of the child provides databases on key indicators for Chilean children's wellbeing. [52] • The department of health statistics and information also maintains

	In exchange, a legally binding agreement between local and national MoHs ensures the supply of high quality data. • Systematically monitors performance in different indicators early detection of pregnancy, obstetric care, prenatal care, immunization coverage, and reproductive health [43]. • Argentina is also part of the NIHCD's maternal new-born health registry global network, the source of several global studies on maternal and neonatal mortality [44-50]		• The SUIN database holds 10 years of data on health, nutrition, education, recreation and sport and protection for Colombian children at national and municipal levels.	data on birth statistics, birth indicators and birth charts.
Limitations/Challenges	Challenging to reach remote areas and those that do not register for health benefits [43,53].	• As in many information systems, the quality and completion of data is very much dependent on the person in charge of updating the system with the most appropriate information. • The huge number of municipalities (over 5000) in Brazil poses a limitation in terms of the homogeneity of the data quality and completion recorded in the system.	Reports with lots of tables but only superficial analysis.	High maintenance

EMR: Electronic medical records; ICBF: Institute of Family welfare; LatAm: Latin American; MI: Myocardial Infarction; MoH: Ministry of health; PNEN: Pré-Natal e Nascimento; SIDRA: Sistemas de Informacion de la Red Asistencial / Information Systems Healthcare Network; SISA: System of Health Information Systems; SUS: Sistema Único de Saúde; SISPRENATAL: Sistema de Acompanhamento da Gestante; SISPRO: Integral Information System of Social Protection; SIDRA; SUIN: Unique Child Information System of the National Family Welfare System; TB: tuberculosis WB: world bank

Table 2: Summary of uses of real world evidence in four Latin American countries

Uses	Argentina	Brazil	Colombia	Chile
Regulatory setting and pharmacovigilance	• Rarely used in marketing authorization decisions • Argentina's Food, Drug and Health Technology National Agency (ANMAT) manages national pharmacovigilance systems to detect and prevent treatment-related AEs. • The ANMAT post-authorization surveillance procedure (provision 8054/10) requires AE and quality data to be collected during commercialisation, and any subsequent corrective action to be taken[54]. • This enables the early detection of AEs during normal use to ensure real-world safety and effectiveness[54].	• The Brazilian National Health Surveillance Agency (ANVISA) execute sanitary control of the production, marketing and use of products and services subject to health regulation [55]. • ANVISA's techno-vigilance system collects data on AEs and technical complaints related to health products in the post-marketing phase of a product [56]. • Before granting authorisation, ANVISA requires an economic information report from product developers, including both international and local RWE [57].	• INVIMA, Colombia's National food and Drug Surveillance Institute (formed under the MoH in 1992) is responsible for inspecting the marketing and manufacturing of health products, implementing health standards and practices for medical approval of import or export products[58]. • Regulations are in place to oversee the registration, marketing, and surveillance of production, processing, uses, and maintenance of medical technologies [59].	• The National Centre of Information on Pharmaceuticals and pharmacovigilance, part of the National Drug Regulations Agency (ANAMED), is responsible for the prevention, detection and research of medicinal products-related AEs [60] • RWE is therefore used to inform ANAMED of a new drug's safety profile post-commercialisation. • This requires the collaboration of the Institute of Public Health, hospital staff (public and private) and the manufacturers of devices, importers and patients[61]. • Medical product manufacturers are required to ensure medical devices meet safety and effectiveness requirements and maintain data to support this through post-market surveillance[61].
HTA decisions (involving HTA Agencies and manufacturers)	• Several official or academic HTAs exist in Argentina (UCEETS, the Institute for Clinical Effectiveness and Health Policy, the HTA Direction within ANMAT, the IMSSET in UBA and the	• The National HTA agency (CONITEC) was formed in 2011 to define the criteria for HTA submissions to the public health system and to develop clinical guidelines [63].	• The Colombian HTA agency (IETS) was established in September 2012, and is responsible for the development and appraisal of evidence-based clinical guidelines, economic evaluations and	• A 2015 law for funding high cost drugs prompted the establishment of a comprehensive HTA process [66] • In response, economic modelling is more frequently used, improving the capacity

	CETSA in iSalud) that have used RWE in their submissions. However, these evaluations were not binding until recently • Formal HTAs are required for health technologies that are to be included in the compulsory benefits packages (PMO or SUR) since MoH resolution of May 2017. This is expected to promote an increase in RWE-based economic evaluations [62]. • The pharmaceutical industry has funded a number of cost-effectiveness studies using RWE, albeit limited.	• RWD is frequently used in CONITEC submissions, in particular epidemiological, resource use and treatment data sourced from DATASUS [64]. • Observational studies, including chart reviews and non-randomized trials were used to support decisions, and surveys were used to identify treatment patterns [64]. • Between 2011-2014, 88.2% of submissions included RWE [15], however, most economic models were based on expert opinion and lacked RWE [15]. • There is a lack of RWE on national burden of diseases, which impairs appraisal decisions [15]. • To submit technologies for reimbursement on the 'expensive drugs', producers must submit a dossier including RWE data (as described above) to CONITEC [63].	budget impact analyses. • The IETS is described by the OECD as "one of the most advanced HTA agencies in Latin America" with a transparent and collaborate process of conducting cost-effective analyses [65]. • Drug costs data from the 2007 SISMED project, which can be freely accessed online, are used across Latin America in modelling exercises and budget planning [18].	to integrate RWE into HTA submissions [66]. • It is expected that the Chilean coverage system will trigger more RWE to be produced and used in HTAs. • Economic evidence is currently being produced mostly with international data, though local registries are also used to estimate cost and resource consumption.
Academic institutions multiple uses	• The institute for Clinical Effectiveness and Health Policy (IECS), based at the University of Buenos Aires, conducts research on the clinical, economic and social impact of health care drugs, practices and	• DECIT – CGATS is a public-sector collaboration between the department of science and technology and the MoH. This public organisation collaborates with research institutions and public	• Government managed national databases for oral health, mental health and other disease groups are freely accessible to researchers. • A national cancer information system collects	• Following the legal boundaries on access to patient data, academic institutions may access RWE only if conducting research that will be contribute to the improvement of public health and maintains patient

	services. • The IECS has a department dedicated to data collection system design, database quality control and statistical analyses, demonstrating the capability to generate and analyse RWE [link]. • Other academic institutions such as the Center for the Evaluation of Health Technologies (CETSA) and the Medical Institute for Social Security and Health Technology Assessment (IMSSET) conduct research using RWE for scientific dissemination as well	universities to review HTA studies. • DECIT – CGATS fosters RWE research by developing monitoring systems for emerging technologies and guidelines to evaluate medical devices [67].	data on mortality, incidence, services and inequality at both a local and national level, but some regions demonstrate under-coverage and there is a lack of peer-reviewed literature on existing data [68]. • Researchers are increasingly accessing and analysing data both from Colombia's compulsory registry Sivigila and the SISPRO information system project [69,70].	confidentiality [71,72].

ANAMED: National Drug Regulations Agency; ANMAT: The Food, Drug and Health Technology National Agency of Argentina (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica); ANVISA: Brazilian National Health Surveillance Agency; CONITEC: National Committee for Health Technology Incorporation (Comissao Nacional de Incorporaca de Technologias); IECS: The (Argentinian) institute for Clinical Effectiveness and Health Policy (Instituto de Efectividad Clinica y Sanitaria); IETS: The (Colombian) agency of health technology assessment (Instituto de Evaluación Tecnológica en Salud); PMO: Plan Medico Obligatorio; RedARETS: the Argentine Public Network for HTAs (Red Argentina Pública de Evaluación de Tecnologías Sanitarias); RedETSA: HTA Network for the Americas (Red de Evaluación de Tecnologías en Salud para las Américas); SUR: Sistema Único de Reembolso; UCEETS: The HTA Coordination Unit of the Ministry of Health (Unidad Coordinadora de Evaluación y Ejecución de Tecnologías en Salud)

7. *Appendices*

Appendix 1

Table 3: Workshops Program and Attendees

Country	Argentina	Brazil	Chile	Colombia
Time and Place	Buenos Aires, 18th October 2016	Sao Paulo, 16th September 2016	Santiago de Chile, 20th October 2016	Bogotá, 24th November 2016
Opening and first Presentation Nahila Justo (Karolinska Institute, ICON). Q&A and open discussion.	Introduction, Objectives and Agenda. First presentation with basic concepts and a situational analysis of the region based on desk research and interviews. Title: "What is RWE and how is it used? Why is it so relevant now? What is the current state of affairs in the Latin-American region?"			
Second Presentation by Michael Drummond (University of York). Q&A and open discussion	The international perspective with case studies and key learnings was introduced in this presentation titled "Generation and Analysis of RWE: Challenges and Opportunities. The Global Landscape"			
Third Presentation: Country-specific perspective introduced and discussed by country Experts	**Sebastián García Martí** introduced several examples including Program "Sumar", the Health Technology Tutelage System, PAMI's CDI Registry and two studies on the Impact of Vaccination Impact conducted by IECS and the "Italiano" Hospital	The local perspective was discussed among attendees to the workshop and much of the interest focused on DATASUS and clinical guidelines	**Manuel Espinoza Sepulveda** presented the local perspective including uses of RWE for HTA purposes, the current state of affairs of the SIDRA project and other relevant initiatives.	**Diego Rosselli** presented local experiences and granular information on a good local example of accessible Colombian RWE (Data from Cuenta de Alto Costo)
Attendees	Representation from government entities such as the Ministries of Health (National, CABA, Santa Fé and Neuquén), the Superintendence of Health Services, and ANMAT; from public and private HMOs (PAMI, IOMA, Medife, Osplad, OSDE, Medicus, Galeano, Omint, OSPIM); from education and research (CETSA Isalud, IECS, OBIME Maimónides); and members of professional associations (CAEMe, CENEXA, INC)	Academia, physicians, healthcare providers and other stakeholders (ICESP, Hospital Infantil Darcy Vargas, Hospital Santa Paula, Sao Paulo Secretary of Health, UNIMED, Instituto de Saúde, Universidade Estadual Paulista Júlio de Mesquita Filho, Magara, PLANSERV, Kantar Health, BSI,	Representatives of the National Health Fund (FONASA), private insurers (ISAPRES), Ministry of Health. Academia and health providers either public or private.	Representation from government entities like Ministry of health, National Cancer Institute, National Health Institute, the Colombian Association of Hospitals and Clinics (ACHC), HMOs in Subsidized and Contributive regime (Gestarsalud, Sanitas EPS), Audifarma Research Group (logistic operator) and Javeriana University

Appendix 2

Table 4: Database mapping search string

CAB Global Health Database Guide 1973 to 2017 Week 48			
Ovid Medline (R) Epub ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, Ovid MEDLINE and Versions(R)			
Search conducted December 12, 2017			
#	**Search**	**Search term**	**Number of hits**
1		(national or nationally).ti,ab.	578770
2		population level.ti,ab.	19712
3		(multinational or multinationally or multi-national or multi-countr$3 or multicountr$3).ti,ab.	11145
4		(regional or regionally).ti,ab.	276742
5		(country-wide level or country level or country population).tw.	3001
6		nationally representative sample.tw.	10277
7		regionally representative sample.tw.	30
8		population-based.ti,ab.	155441
9		Global population$1.tw.	3222
10		Continental Population$1.tw.	281
11	General/population	or/1-10	987873
12		database$1.ti,ab.	404583
13		(register$1 or registry or registries).ti,ab.	191602
14		(real world or real life or evidence based data).ti,ab.	45907
15		(national program$1 or health program$1).mp.	66624
16		claim$1.ti,ab.	74333
17		(electronic medical record$1 or medical record$1 or health record$1).ti,ab.	122789
18		*Population Surveillance/ or (Health surveillance or population surveillance).ti,ab.	26694
19		*Information Systems/ or Information System$1.ti,ab.	46090
20		*Health Surveys/ or exp Health Care Surveys/ or (health adj2 survery$1).ti,ab.	45213
21		*Health maintenance organization/ or Health maintenance organi?ation$1.ti,ab.	13616
22		dataset.ti,ab.	50380
23	Data sources	or/12-22	995158
24		11 and 23	184126
25		observational.ti,ab. or Observational Study/	191662
26		non interventional.ti,ab.	2171
27		*retrospective studies/ or retrospective.ti,ab.	505817
28		*prosepctive studies/ or prospective.ti,ab.	601885
29		*cohort studies/ or cohort.ti,ab.	543447

30		*cross-sectional study/ or cross-sectional.ti,ab.	381490
31		*longitudinal study/ or longitudinal.ti,ab.	252406
32	Study design	or/25-31	1996308
33		24 and 32	59301
34		cost$1.ti,ab.	572023
35		(quality of life or QoL or HRQoL).ti,ab.	269257
36		(treatment$1 or prescription$1 or prescribed or drug$1 or medicine$1 or medication$1).ti,ab.	6340663
37		*incidence/ or incidence.ti.	119848
38		*prevalence/ or prevalence.ti.	172441
39		*morbidity/ or morbidity.ti.	38392
40		*mortality/ or (mortality or death or dead or die).ti.	279377
41		(life year$1 or survival).ti,ab.	954402
42		comorbidit$3.ti,ab.	110699
43		(adverse event$1 or safety).ti,ab.	624218
44		(hospitali?ation$1 or admission$1).ti,ab.	364490
45		risk factor$1.ti,ab.	662739
46		patient outcome assessment$1.ti,ab.	21
47		generic measure$1.ti,ab.	786
48		effectiveness.ti,ab.	461426
49	Data types	or/34-48	8793013
50		33 and 49	42667
51		crossover procedure/	0
52		single blind procedure/	0
53		randomized controlled trial/	543455
54		double blind procedure/	0
55		randomi?ed controlled trial.ti,ab.	96619
56		randomi?ed clinical trial.ti,ab.	31004
57		random$.ti.	229593
58		(crossover* or cross over*).ti.	14837
59		(((doubl* or singl*) adj blind*) or clinical trial).ti.	84824
60		(case report or news or comment* or letter or rat or rats or mouse or mice).ti.	1893459
61	Irrelevant publication types	or/51-60	2568964
62		50 not 61	41783

63		limit 62 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or erratum or letter or note or "review" or trade journal or addresses or autobiography or bibliography or biography or case reports or clinical conference or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comment or congresses or consensus development conference or consensus development conference, nih or controlled clinical trial or dictionary or directory or duplicate publication or festschrift or guideline or historical article or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or meta analysis or news or newspaper article or patient education handout or periodical index or portraits or practice guideline or pragmatic clinical trial or published erratum or randomized controlled trial or "research support, american recovery and reinvestment act" or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or retracted publication or "retraction of publication" or "scientific integrity review" or systematic reviews or technical report or twin study or validation studies or video-audio media or webcasts) [Limit not valid in Books@Ovid,Global Health,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	19832
64	Excluding irrelevant publication types	62 not 63	21951
65	limit to humans	limit 64 to humans [Limit not valid in Books@Ovid,Global Health; records were retained]	17471
66	limit to latin america or case study countries	(Latin americ$ or south america$ or argentin$ or brail or colombia$ or chile$).ti,ab.	106924
67		65 and 66	121
68	Studies published from 2007 onwards	limit 67 to yr="2007 -Current"	114
69	**After de-duplication**	**remove duplicates from 68**	**96**

Appendix 3

Table 5: Databases by geographic region, scope and database type

Data sources by geographic region			**Database coverage (n)**				
Country	n	(%)	International	National	Regional	Local	Not reported
Argentina	44	11%	7	9	5	23	0
Brazil	240	59%	3	57	57	123	0
Chile	62	15%	2	21	4	35	0
Colombia	46	11%	0	16	9	20	1
Latin America (non-specific)	15	4%	12	2	0	0	1
Data sources by database type			Database coverage (n)				
Database type	n	(%)	International	National	Regional	Local	Not reported
Administrative	66	14%	2	11	5	47	1
Clinical / registry data	190	43%	11	16	26	136	1
National Health Information & surveillance Systems	151	42%	11	78	44	18	0
Total included articles	46	100%	24	105	75	201	2