Access to Medicines in the United Kingdom: Systematic Review of Literature between 2008-2018

ABSTRACT

Background: Budgetary constraints and the rising cost of new innovative medicines are the key challenges for access to medicines. Multiple research studies explored diverse dimensions of this topic, however, a thorough and detailed review of existing literature on access to medicines in United Kingdom is lacking. Therefore, the objective of this systematic review of literature was to critically review and analyse the literature pertaining to original research on access to medicines issue in the United Kingdom. This review includes two types of studies: (a) UK centric studies (b) studies comparing UK with the other countries.

Methods: A systematic search of articles published between Jan 2008 and 12 October 2018 was conducted according to PRISMA guidelines using the following databases: PubMed, Scopus, Science Direct, and specific journals including BMJ, Lancet, Value in Health, Pharmacoeconomics, Pharmacoeconomics Open, Journal of pharmaceutical policy and practice, Health Policy.

Results: The searches across all databases and journals resulted in 53 relevant articles. The data extracted from the 53 articles generated key themes. These themes included: Access to Medicines, Health technology assessment (HTA), Pricing and Health technology assessment, Risk Sharing Agreements & Stakeholders involvement/ views on reimbursement Process. Subthemes were added under the key themes where applicable.

Conclusions: This review systematically evaluated the current literature and identified variability in access to medicines across countries in UK &EU and across different categories of medicines. Medicine licensing and reimbursement environment is continuously evolving and there are challenges as well as opportunities for learning and collaboration among countries which are at different stages of advancement in their systems.

I. Introduction

Access to Medicines is linked to the availability and also the financial and physical ability of an individual to obtain and receive medicines and this is an essential element to attain the best possible standards of health. [1][2]

Access to medicines is a problem not only limited to poor countries or neglected diseases but a global problem affecting people in rich and poor countries alike.[3] Approximately one-third of the world's population lack access to essential medicines [4] Although developed regions like Europe promise towards WHO goals for Universal Health Coverage, people with lower income are 5 times more likely to perceive access as a barrier [5].

There are various factors which influence access to medicines; key impacting challenges include budgetary constraints, increasing cost and ageing populations. [6]. The increasing cost of medicines worldwide could become a major barrier to access to medicines. [7]

The United Kingdom (UK)'s healthcare system is largely public, as 80% of funding is sourced from taxation, 12% from national insurance, 4% from other charges and miscellaneous, 3% from Trust interest receipts and 1% from capital receipts. Unlike US, UK has relatively low private insurance coverage. Role for private healthcare in the UK is now increasing. [8] After the medicine is licensed in the UK it can be used by prescribers in the National Health Service (NHS), though NHS and prescribers will choose to await official guidance on its use. The purpose of this guidance is different to that of licensing, which considers efficacy and safety. Though NHS guidance does study the efficacy of the medicine, it also reflects on its clinical and its cost effectiveness. There are different bodies (National Institute for Health and Clinical Excellence (NICE), All Wales Medicines Strategy Group (AWMSG), Scottish Medicines Consortium (SMC) & The Department of Health, Social Services and Public Safety in Northern Ireland) across the UK which produce guidance for the use of medicines in the NHS. [9]

The United Kingdom (UK) has been a leader in life sciences sector and approximately one-eighth of the frequently prescribed medicines in the world have been developed in the UK [10]. However, it has been argued that the UK is relatively slow at reimbursing new medicines when compared with the other EU countries. [11]

Multiple studies have explored diverse dimensions of this topic i.e. access to medicines in UK. Varnava et.al[12] examined the medicines appraisal process in Wales and compare its processes and recommendations with the two other UK health technology appraisal bodies. Charokopou et.al [13] investigates the impact of evidence submitted for reimbursement assessment on HTA recommendations in Scotland. A study by Bourke et.al[14] has assessed whether there is a UK societal preference to support current NHS policies associated with the funding of treatments for rare diseases. Alam et. al study [15] analyse the relationship between changes in prescription co-payments and changes in dispensing rates in Wales. This systematic review also includes studies where UK has been compared with the other countries.

Despite availability of multiple studies currently there is no thorough systematic review of existing literature on broader access to medicines issues in the United Kingdom. Hence in this context, this review has been performed. The aim of this this systematic review of literature is to critically review and analyses the original research articles on the broader issue of access to medicines in the UK (England, Wales, Scotland & Northern Ireland). The access articles also include articles related to medicines access, medicines availability, medicines funding, HTA

impacting access and medicines regulation. The review also identifies gaps in the existing literature and make recommendations for future research.

II. Methods

Scope of review: Inclusion and exclusion criteria

Access is an important concept in health policy and health services research, yet it is one which has not been defined or employed precisely. To some authors "access" refers to patients' ability or willingness to enter into or use of the health care system, while to others it characterizes factors influencing entry. The theoretical framework for study of access to medicines was developed from the concepts of Penchansky R, Thomas JW (The concept of access: definition and relationship to consumer satisfaction.) and from the WHO's access definition Australian National Medicines Policy (2000). Access is presented as a broad concept that summarizes a set of aspects including availability, accessibility, acceptability affordability, Pricing and reimbursement. This forms the basis of selecting and including studies for this systemic review.[16,17] Based on the chosen framework this review includes all related studies which either analyse access (perceived /actual) or discuss any of the aspects that contribute to the concept of access.

This systematic review follows PRISMA guidelines as shown in figure 1. Two investigators applied the eligibility criteria to examine the titles and abstracts of the original articles.

The articles were selected on the basis of the pre-defined inclusion/exclusion criteria, which were formulated to reflect the objectives of the review. Inclusion criteria specify original research full text papers on access to medicines which were UK centric as well as the papers which were comparing the UK with the other countries. Articles were required to be in English with publication date between 1st Jan 2008 to 14 Oct 2018. The search was restricted to the studies relating to humans and original research articles. Titles and abstracts were screened to eliminate the studies that were not relevant to the objectives of the review. In the end only full texts of the remaining studies were analysed.

Search strategy

This review used systematic searches to identify scholarly articles which were published between 1st Jan 2008 and 14 October 2018. Purposefully the search strategy was designed to keep it broad, to make sure that all relevant articles are being included. The databases searched included: PubMed, Scopus, Science Direct, and specific journals including BMJ, Lancet, Value in Health, Pharmacoeconomics, Pharmacoeconomics Open, Journal of pharmaceutical policy and practice, and Health Policy.

Search terms were combined and integrated for the selected database and journal searches. Three combination of terms were used. "Boolean Operator" rules were applied for the conducted searches. To combine the key terms Boolean operator 'AND' was used. Boolean operator 'OR' was used to remove search duplication where possible Wildcard (*) was also used to maximize search results. Search terms (title, abstract, text, keyword) were combination of access OR availability OR affordability OR funding OR cost* OR pric* OR reimbursement AND drugs OR medicine* OR pharmaceutical* AND United Kingdom OR UK OR England OR Wales OR Scotland OR Northern Ireland. Reference lists at the end of selected articles were assessed to find out additional original

articles that standard searches could have missed. A description of the search strategy is included in the Appendix 1.

Data extraction and synthesis

After identifying possible studies, the primary investigator (NA) screened all retrieved titles to ascertain their potential relevance. An extraction table was prepared which included study characteristics from all relevant studies. Lead author (NA) extracted the data and discussed the discrepancies (if any) with the other researcher (ZUDB) when required. The extracted information included Author name & year of the publication, data collection period, journal, aims/objectives, methods, study findings.

The synthesis of the articles was performed to identify themes. The paper analysed two types of studies: (a) UK centric (b) papers comparing UK with the other countries. As there were large number of papers on the latter they were included in the results and synthesis, thus allowing to explore commonalities and differences across different countries on access to medicines in Europe including UK.

Assessment of quality and risk of bias in included studies

The lead author (NA) independently assessed the quality of each of the original article included in this review and to achieve consensus discussed the assessments with the second author. The modified Newcastle-Ottawa Scale (NOS)[18] was selected as it was found relatively easier to use and reliable to measure biasness in the original research articles. Each of the selected original article was assessed for the organisational characteristics (e.g. HTA or NHS), data source (e.g. database or questionnaire-based), intervention description (e.g. MEA), comparability (e.g. UK vs. EU), assessment of outcome (e.g. QALY or preferences), and data presentation (e.g. percentage, median). The lead author appraised each article using the Newcastle-Ottawa Scale assessment methods. Based on the overall score on the Newcastle-Ottawa (NOS) scale, articles were classified as ""good quality" (5-6) points. “fair quality" (3-4 points) or poor quality" (0-2 points). Based on the results of quality assessment 44 articles were classified as good quality and rest of the articles were of fair quality.

III. Results

The search yielded 20,097 titles (PubMed n=4291, Scopus n=6707, Science Direct n=1363, additional records through Journals, n=7736). After removal of irrelevant and duplicate records, 1240 abstracts were screened. Of these, 1142 studies were excluded. Of the remaining 98 articles, 45 were excluded as they did not describe access to medicines or did not illustrate or focussed on UK (**Figure 1**).

Out of 53 articles, 17 were UK centric while 36 were multi-country comparative studies, in which the UK was compared with the other countries. The data extracted from the 53 articles generated key themes. These themes included: Access to Medicines, Health technology assessment (HTA), Pricing and Health technology assessment, Risk Sharing Agreements & Stakeholders involvement/ views on reimbursement Process. Number of articles under each theme were as below.

Access to Medicines: 6

Health Technology Assessment: 33

Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements: 7

Pricing: 2

Stakeholders' involvement/ views on Reimbursement Process: 3

Subthemes were added under the key themes where applicable. See Appendix 2 for extracted data from individual study included in this review.

Characteristics of the studies

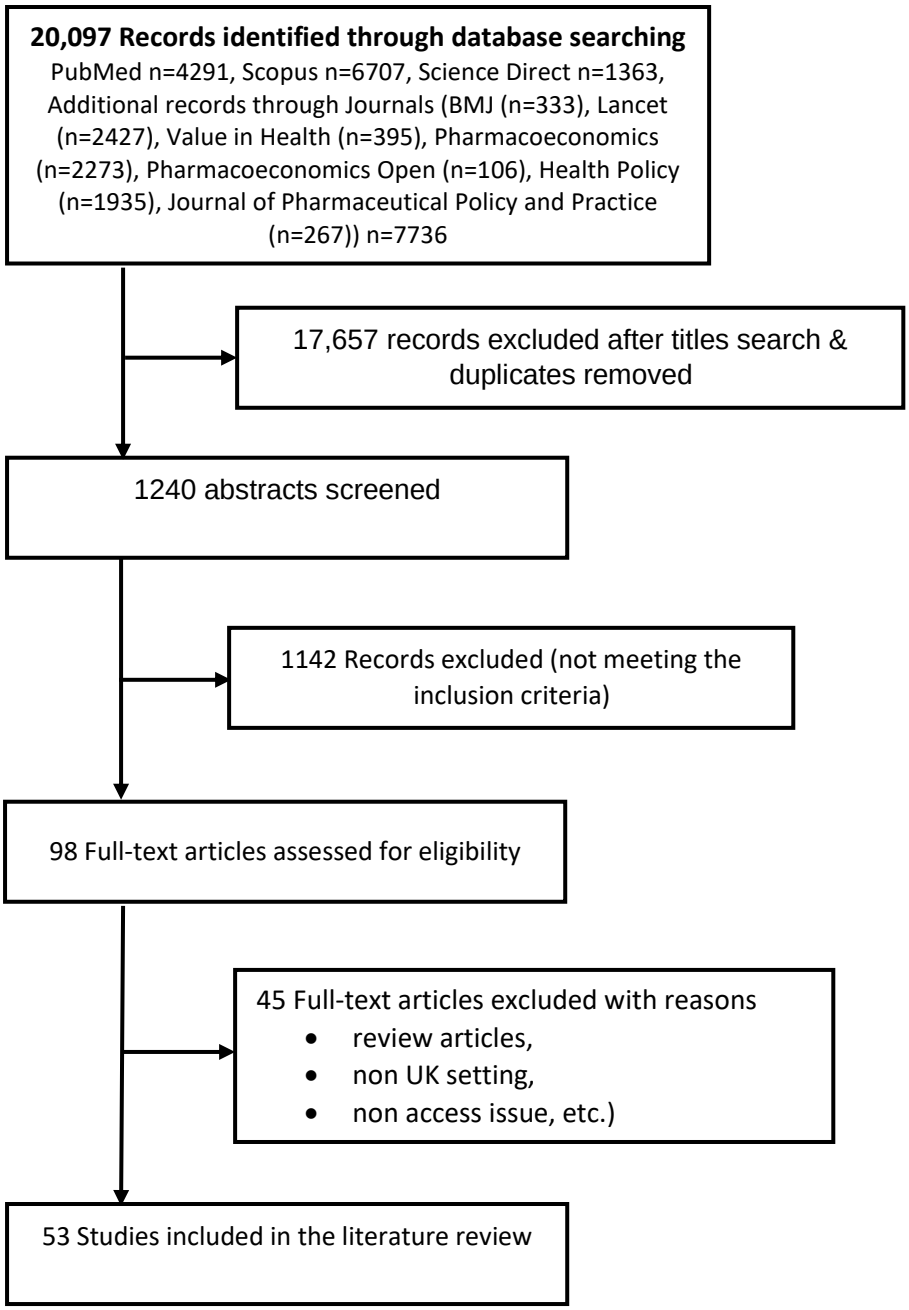

Figure 1: Study selection process (PRISMA)

Access to Medicines in the UK and Europe

Europe is one of the most developed region in the world that has shown greater promise towards WHO goals for universal health covergae. Cylus & Papanicolas,[5] examined peoples' perceptions regarding access to medicines across EU and found substantial variability of access to medicines in the region.. Other factros including the standard of care and long queues for heatlh services also possibly contributed to this hinderance. It was observed that poor standard of care and long waiting queues limit access to healthcare services including medicines. Primarily these factors contribute to accessibility issues for patients irrespective pf their income levels but could

become affordability issue for low income patients as they have to pay high out of pocket costs and to seek care in the private sector. [5]

It was observed that the patients' access to medicines can be greatly influenced by the decisions from the reimbursement bodies. Ragupathy, et al; [19] compared access in terms of the number of medicines, time since registeration of the medcines and the number of innovative medicines which are authorized and funded in the US, the UK, Australia and the New Zealand. Study indicates that the UK's National Health Service (NHS) funded relaively more medicines, the newest medicines and the most innovative medicines. [19]When compared with the France, Germany, and the United Kingdom (UK), Japan was found to have relatively higher health insurance coverage and fewer barriers towards access. In Japan time lag between granting of licence and the start of reimbursement was 66 days. However, this time was reported as 120 days in Germany & UK. In terms of prices of drugs, considerable differences were not observed between Japan and the selected EU countries.[20]

Variability in access to medicines is driven by many factors, one of which is time to entry of new medicines in the individual European countries. In a study by Ferrario [21] time to entry of cancer medicines in selected EU (Belgium, Estonia, Scotland, and Sweden) countries was analysed. Results of this study indicates that shorter time intervals from authorization to submission for reimbursement, presence of a local sales representative of manufacturer, prelaunch evidence of added clinical value and a short time gap since EU-wide marketing authorization increases the likelihood of early access to medicines. Early interaction between manufacturers and agencies could help to find medicines likely to have more clinical value. It was observed that the countries with smaller markets like Estonia take more time to launch new medicines.[21]

In patient with rare diseases, access to medicines is variable across Europe and is impacted by high costs, weak evidence related to efficacy/safety and societal preference for funding of orphan drugs. Germany, Switzerland, and France are countries with highest spending on medicines with rare diseases. In the United Kingdom, Germany, Switzerland, France and in the Scandinavian countries, more patients can access medicines for rare diseases in relatively lesser time.[22]

Health Technology Assessment (HTA) in the UK and Europe

Health technology assessment (HTA) has become a critical basis for pricing and reimbursement decision-making and is therefore considered more proximal rather distal determinants towards access.

Factors Influencing HTA recommendations

A review of All Wales Medicines Strategy Group (AWMSG) appraisals has revealed that the quality of the randomized controlled trials (RCT) leads to a substantial impact upon HTA recommendations. Linley & Hughes; [23] stated that this impact on recommendations could be attributed to high quality RCTs attracting a high overall costs resulting in higher incremental cost-effectiveness ratio (ICER) [23]. In another study by Charokopou et al.,[24] it was observed that in Scotland, cost effectiveness analyses is an important factor for Scottish Medicine Consortium(SMC) reimbursement recommendations.

HTA recommendations impact on budget, usage and cost effectiveness

Analysis of HTA decisions in context of their impact on patient access is of great importance. Neill & Devlin, [25] has introduced a tool for meauring the level of patient access related to various types of NICE (National Institute for Health and Care Excellence) decisions , mainly restrictive ones. These estimates of access level are not fully robust but still a useful way of presenting HTA decisions. [25]A study by Mauskopf et al;[26] examining impact of the NICE restrictive recommendations for medicines confirms a substantial association between the financial impact to the NHS and magnitude of restrictive decisions by NICE. [26]

A study by E.S. (2009) [27]examining NICE's HTA decisions confirms that negative and restrictive HTA decisions don't essentially have an impact on lowering prescription rate and cost. This lack of impact could be due to lack of adherence with HTA recommendations at the level of prescribers. This could also be due to difference in objectives of the decisions makers in HTA bodies and local health service. For a considerable decrease in prescription rates & cost, it is esstential to improve the prescribers' compliance with the HTA decisions. [27][28]

A study by Hoyle [29] denies the assumption that price of drug rises with the rise in inflaction. The study indicates that drugs were assesed to be more cost effective when compared with the NICE assessment results in the past. Hence there is a possibility that some of the NICE decisions with negative or restrictive outcome in the past could have resulted as positive deicisons.[29]

Comparison of practices, processes and policies of assessment

A comparative study by Angelis et al; (2018) examining the practices, processes and policies of value-assessment for new medicines across eight European countries (France, Germany, England, Sweden, Italy, Netherlands, Poland and Spain), identified that all countries assess same kind of evidence. However, the specific criteria and endpoints used, required level of evidence, and the way they are incorporated varies across countries are generally unknown. Incorporation of additional 'social value judgements' beyond clinical and economic evaluation could help explain heterogeneity in HTA recommendations and decision-making. More comprehensive and systematic assessment measures characterised by improved transparency, in terms of selection of evaluation criteria, their importance and intensity of use, could lead to more balanced evidence- based decision-making. This could possibly improve efficiency in resource allocation, while also raising public confidence and fairness. [30]

A study by Lebioda et al; [31] explored the significance of indirect comparisons in the German early benefit assessment of new drugs and other HTA processes in England, France and Scotland. The gold-standard to compare efficacy, effectiveness and safety are head to head studies but in absence of these head to head studies, indirect comparisons are done. The study indicates that a comparison of the different HTA bodies regarding the indirect comparisons is challenging and it is evident that pharmaceutical industry struggles to implement indirect comparisons due to tough requirements. [31]

A study by Kolasa & Wasiak, [32] comparing Scotland and Poland HTA process indicate that Polish HTA agency, Agencja Oceny Technologii Medycznych (AHTAPoL), issues more negative recommendations than Scottish Medicines Consortium (SMC). In Poland grounds for negative recommendations were mostly due to clinical and or safety reasons while the lack of cost effectiveness was a key reason for negative recommendations in Scotland.

SMC was found to endorse restrictive use where negative recommendation was made by AHTAPoL. The study also observed that the Scottish HTA methodological guidelines were more informative with regard to details on clinical and economic evaluations. [32]

A study by Bending et al; [33] comparing reimbursement systems in France and Scotland reveals that French agency Haute Autorité de Santé (HAS) recommend medicines more often than SMC. Some of the differences in the recommendations are possibly related to local clinical guidelines and choice of the comparators. SMC is challenged with a price set by manufacturer and its reimbursement decisions are based on clinical and economic evidence. HAS makes reimbursement decision based on clinical evidence and price is set separately through CEPS (Comité économique des produits de santé) discussions. Above two approaches offer different incentives for the manufacturers. France may offer more sales in terms of volume at a lower price while Scotland manufacturer might have relatively high price but lesser sales volume due to restricted use. This study provides some useful descriptions for the variations observed in the recommendations for particular set of medicines. However, the variations could be connected with other factors like, politics, social traditions, and prescribing patterns. [33]

A study by Vega et al; [34] comparing HTA processes and listing decisions across four countries (Australia, England, Netherlands, Sweden) indicates public guidance for health technology evaluation is available in all four countries and these evaluations are based on the manufacturer submitted evidence. England also engage therapeutic assessment groups for independent assessments. In England there is readiness to pay for an explicit ICER threshold. HTA listing recommendations are relatively high in all four countries but there is variability across various settings. Study shows poor to moderate agreement on the listing decisions. This difference could be related to the timing of the HTA assessments, status of medicines (Orphan vs non-Orphan), categories of medicines offering low value for money, difference in the HTA processes, variations in how the submitted evidence leads to evaluation, difference in national preferences, regulatory structure and overall decision-making process. Further research is required to investigate if overall appraisal process reflect social values [34]

A study by Spinner et al., [35] comparing HTA processes in England, Wales, Australia and Canada provides an analysis of the variability in the clinical evidence considered by different HTA agencies and resulting reimbursement decisions. Study results indicate that HTA bodies made the same decisions on 4 occasions and different decisions on five instances. Each HTA body base their decisions using different types of evidence such as efficacy and/or cost effectiveness. HTA bodies considered overlying sets of comparators and trials when appraising the same medicine. While PBAC (Pharmaceutical Benefits Advisory Committee) and NICE considered indirect and/or mixed comparisons, however Canadian CDR (Common Drug Review) did not. In some studies, CDR and/or NICE omitted trials from review if the medicine and/or the comparator were not used according to the relevant approved license. In the listing recommendations reviewed, considerable variability exists in the clinical evidence considered by PBAC, CDR, and NICE for drug-listing recommendations. Differences in evidence resulted from differences in the consideration of treatment comparison data and differences in medical practice in each country. [35]

A study by Beletsi et al; [36]comparing various EU HTA bodies at different levels of maturity in the application of HTA indicate that the evaluation criteria in all countries include effectiveness, safety, relative effectiveness, and economic data. In group of countries including England which are relatively advance in HTA implementation, the key aims are to improve quality of care, equal access, and use of resource efficiently. Relatively less advanced countries have established HTA organizations and guidelines but often pursue the recommendations of other countries at advance stage of implementation. These countries put more weight on the budget impact of new medicines and use of HTA as a tool for cost estimation. HTA bodies have been established in developed countries as well as in less resourceful countries. Countries considering developing an HTA body can use the experience of other countries at different stages of HTA implementation. [36]

In Europe, two contrasting HTA approaches work for assessing the value added by new medicines. In some countries including the UK, the price of, and access to, a new medicine has to be justified by the health gain it delivers compared with existing treatments, usually articulated in quality-adjusted life-years (QALYs) gained. In other countries including France, the assessment of added value is based on an assessment of the clinical outcomes as compared with existing treatments. Drummond et.al; [37] assessed the pros and cons of England vs France approach, both in terms of the assessments they produce and the efficiency and practicality of the process. The assessments of the value added by new medicines in England and France were found similar. However, approach followed in England is considered extra transparent and creates more political deliberation. Both approaches are appearing to converge, with England confidential price negotiations and France announcing new requirement to estimate cost-effectiveness. [37]

Framework to Study HTA recommendations

While improving access to medicines is a priority at various countries level, differences in the HTA recommendations is one contributing factors towards gap in access to medicines. Hence it is important to comprehend the reasons for differences in decision making process. A study by Nicod & Kanavos, [38] had proposed and steered a well-structured framework aiming to explore the variability in HTA recommendations across settings. This framework is thorough and provides understandings into decision-making practices for the selected case studies.[38]

Comparison of HTA Recommendations in UK and Europe

Varnava et al; [12]observed that patients in wales have relatively faster access to new medicines over those in the England. All Wales Medicines Strategy Group (AWMSG) follows The National Institute for Health and Care Excellence (NICE) guidance if available. However, for the medicines where NICE guidance is not available, AWMSG assess the medicines and its decisions are superseded if NICE guidance becomes available anytime later. According to Varnava et al; [12] overall decisions across HTA organizations in United Kingdom are very similar.

Barbieriet al; [39] noted that in comparison to Scottish Medicine Consortium (SMC), NICE recommendations are relatively more restrictive . SMC appraises all new medicines whereas NICE appraises a narrower selection of new medicines. Scottish Medicine Consortium base their evaluations on manufacturer submissions while NICE uses manufacturer as well as third-party assessments. Third-party assessment has its merits, but it could add to the

budget and could take more time and hence a mix of both approaches is a way forward. [39]

A study by Allen et al;[40] compared the Canadian national HTA recommendations with the other HTA bodies in Australia, Canada, England, and Scotland, and identify factors for differing HTA recommendations. HTA bodies are also found to share some similarities, including a focus on clinical efficacy and cost-effectiveness in their decision-making processes. The differences in recommendations could be considered to be due to an organisational approach to risk perception, and the comparator choice used in clinical and cost-effectiveness studies. Examples in which new medicine have received negative recommendation because of uncertainties surrounding a range of factors include cost-effectiveness, choice of comparator, clinical benefit, safety, trial design, and timing of submission. This study demonstrates how several factors can impact HTA decision making process and result in conflicting recommendations.[40]

A study by Nicod & Kanavos,[7] analysing HTA recommendations across five countries (England, Scotland, Sweden, Canada, and Australia) highlights the significant differences in the HTA recommendations, suggesting that HTA methods may be influenced by difference in priorities, therapeutic area, levels of evidence, perceptions of value, methods used to address uncertainty, and the capacity and inclination or not to ponder and implement risk sharing agreements. HTA bodies should be clearer about their expectations in terms of whether a manufacturer should prove the new medicine' s relative effectiveness compared to placebo or other treatments as clear guidance could help to avoid unnecessary negative recommendations and re-submissions. Further investigation is needed to better appreciate and measure how the evidence submitted may impact the assessment within different areas of therapeutic use.[7].

A study by Fischer et al;, [41]comparing decisions of HTA body in Germany with HTA bodies in England, Scotland and Australia revealed that German FJC(Federal Joint Committee) significantly deviates in its recommendations from established HTA agencies. While this can be attributed to variability in the mandates of agencies, characteristics and decision-making process as well as the consequences of a negative decision for patient access, this study reveals that the FJC appraisal is found more stringent than NICE. [41]

A study by Vegter et al; [42]comparing HTA recommendations for orphan drugs for rare diseases across Scotland and Netherlands revealed that higher proportion (95%) of orphan drug submissions were approved for reimbursement in the Netherlands, as compared to Scotland (21%). Moreover, cost-effectiveness or cost-utility analyses were included in the majority of (24 of 37) submissions in Scotland, while in the Netherlands this was only included in 1 out of 38 submissions. [42]

A study by Chabot & Rocchi, [43] reviewed and compared Canada and England HTA recommendation's records and the influence of clinical and cost-effectiveness evidence on the HTA recommendations. Study results show an extensive variation in the rate of positive recommendations, ranging from 48% for NICE to 95% for Canada's national process. Interagency agreement on HTA recommendation was also found to be low. Data on survival was not mandatory for a positive recommendation and progression-free survival was found acceptable in some cases. To address cost-effectiveness various approaches were adapted in each jurisdiction subsequent to the HTA process. In such cases NICE was likely to issue a negative recommendation, while Canada's process was most likely to issue a positive recommendation with an obligatory pricing arrangement. [43]

A study by A. Lozano-Bla´zquez et al; [44]comparing the recommendations by HTA bodies in UK & Spain reveals both countries share the same practice as they only appraise carefully chosen medicines. For the medicines assessed by both NICE and Spanish bodies, this study shows that there are more medicines assessed in Spain than by NICE as there are more HTA bodies and their processes are simpler. There are more refusals from NICE than by Spanish Committees. While NICE uses cost-effectiveness thresholds in their appraisals resulting to a 'not recommended' decision in many cases; Spanish bodies are inclined to recommend cancer drugs for subpopulations of patients where better outcomes can be obtained. Spanish Committees take lesser time than for NICE, probably because of the relatively simpler appraisal process in Spain.[44]

Health Economic Evaluation

A study by Skoupá et al; [45] compares data requirements and their availability for health economic (HE) evaluations in five countries in Central/Eastern Europe (CEE) (Poland, the Czech Republic, Slovakia, Hungary, and Romania) and five countries in Western Europe (WE) (the United Kingdom, France, Germany, The Netherlands, and Sweden). The study indicates that the HE evaluations are obligatory in most of the countries for reimbursement applications. Health economic evaluation generally use cost-effectiveness analysis and budget-impact analyses. The preferred outcome of cost- effectiveness analysis is quality-adjusted-life years. In Romania, France, and the Czech Republic, guidelines could not be identified at the time of the survey. In Sweden and the United Kingdom license holder usually prepares HE evaluations dossiers. United Kingdom, Poland, and Slovakia have a clear inclination to pay up to a certain threshold. Some countries (The Netherlands, Sweden, France, and Poland) require a full societal perspective in the CE analysis. There are same requirements for HE analyses in Central/Eastern Europe (CEE) and western Europe (WE), but differences were found in availability of health economics data. In Western Europe data can be acquired easily than in central and eastern Europe. As a result in Central/Eastern Europe (CEE) countries HE evaluation outcomes are impacted because of less precise inputs. [45]

A study by Franken et al; [46] assessing the impact of economic evaluation on medicines in four European countries, ranging from those who have embraced it (England, the Netherlands, and Sweden) to one that has not embraced it (Germany), reveals that health economic evaluation has had little impact on restricting access of expensive medicines. While economic evaluation may have facilitated some countries to negotiate price decreases for some medicines, it has also included the cost discussion in the clinical effectiveness domain. The differences in tactics but similarity in outcomes suggest that health economic evaluation be seen mainly as rhetoric.[46]

Use of Real-World Data in HTA

A study by Makady et al., [47]examining difference across HTA bodies and across time reveals that Real-World Data (RWD) was more frequently included in cost-effectiveness assessments (CEAs) than in Relative Effectiveness Assessment (REAs). Inclusion of RWD in REAs differed between the five agencies, with some citing RWD only for prevalence and/ or incidence, and others for drug effectiveness and safety. Meanwhile, no clear trend in Real-World Data inclusion over time was found. However, these results should be interpreted with caution owing to differences in practices between agencies and varying numbers of reports published every year. Future research should aim to explore RWD inclusion and appraisal within Conditional Reimbursement Schemes

(CRSs) implemented by different HTA agencies, which provide an ideal context for RWD use in HTA practice, and across multiple disease indications. [47]

A study by Makady et al., [48] also reviewed policies of six European HTA agencies on RWD use in REA of drugs. Policies for RWD use differ across HTA agencies. Such variations might discourage the use of RWD for HTA. To facilitate the use of RWD for HTA across Europe, more alignment of policies seems necessary. Recent articles and project proposals of the European network of HTA may provide a starting point to achieve this. The reality of how RWD is used in practice may differ from policies and should be the focus of future research. [48]

Comparative Effectiveness Research (CER)

A study by Sorenson, [49] focussing on the use of Comparative Effectiveness Research (CER) in decisions about drug coverage and pricing in six European countries (Denmark, England, France, Germany, the Netherlands, and Sweden) indicate that in Europe the role of CER has increased in drug coverage decisions and to some extent in deciding prices. While this contributes to evidence-based decision-making, it also helps in finding the medicines offer best value for money. Study indicates that countries adopt various approaches to use CER in drug coverage decisions.[49]

Relative Effectiveness Assessment (REA)

A study by Kleijnen et al., [50] analyse the possible barriers and critical success factors for the implementation of European collaboration in the field of relative effectiveness assessment (REA) of medicines. Study identifies barriers which related to methodology, resources required to adapt at national level and difficulties in its implementation. The factors, which contributed to success for cross-border evaluations were the collaboration of competent partners, quality and timely evaluation. For optimal collaboration more tailoring of the process and methods is required.[50]

A study by Kleijnen et al., [51] compares the guidelines and relative effectiveness assessments (REAs) of medicines for pricing or reimbursement decisions in six EU countries (England, France, Germany, The Netherlands, Poland, and Scotland). Analysis of the guidelines reveals that there is preference for clinically and patient outcomes related end points (Overall Survival (OS) and Quality of Life (QoL)) over surrogate end points. It was found that all REAs include overall survival data if available, but this data is not robust. Majority of the guidelines do not clarify about Progression Free Survival (PFS) and its relevance varies across studies HTA bodies. It was found that 70% of the REAs include PFS data. In 54% of relative effectiveness assessments QoL data was included but had a little influence on the HTA decisions. In EU regulators are now accepting some degree of uncertainty in clinical evidence and this has challenged the HTA decision-making on relative effectiveness of new medicines due to gaps in requested evidence versus available clinical evidence. Study conclude that a multi-stakeholder discussion would help to respond to this challenge. [51]

Pricing

Regulatory approach VS Market Environment Impact on Prices

Prices in an individual country are determined either via regulatory approach or through market mechanisms. In the UK, a more formal regulatory approach is used as NICE uses the cost effectiveness analysis to determine

prices for new medicines. However, prices in US are not controlled and are determined through a free market economy. While value-based pricing in both countries is driven by different mechanisms (regulatory vs market), it cannot be verified that these different mechanisms result in different outcomes.[52]

Reference Pricing and Health technology assessment

To seek better value for money, countries use reference pricing and HTA as a tool for making funding recommendations. However, reference pricing cannot be used in all situations. While Health technology assessment represents a much better approach, reference pricing could assist with pricing and reimbursement of drugs which are offering almost comparable treatment value when compared with currently available medicines. Various EU countries have adopted more than one approach at different times. Drummond et.al; [53] analysed these practices in Germany, The Netherlands, Sweden and the United Kingdom and found that a twofold approach is evolving. This encourage HTA as key policy for assessing value for money which in turn is supported by reference pricing. Netherlands and Germany are the examples of countries heading towards this twofold approach while United Kingdom has relied on HTA policy only.[53]

Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements

Some new and high cost medicines are being authorized to go through risk sharing agreement as relatively low level of evidence (clinical and/or cost effectiveness) is produced. Reimbursement process face challenge while evlauting these medicines due to weak evidence hence final recommendations carry a risk. To address this, risk sharing agreements are being introduced to addresss the uncertainty associated with these risks and to help patient get timely access to these medicines. .[54]

A study by Grimm et al; ,[55] introduces an HTA risk analysis chart which reviews the payer strategy and uncertainty burden (P-SUB) to quantify the risk associated with HTA recommendations. It helps people with decision authority to identify those circumstances by presenting a standardised concept to show the need for and potential value of different types of MEAs. Its use in HTA could make sure that MEAs are considered regularly, constantly and visibly. In the emerging environemnet of pahrmaceuticals, it is believed to be beneficial for both parties; payers as well as for the industry. [55]

MEAs are growing in numbers and it is expected that MEAs will continue to expand in the future. A study by Pauwels et al; [56] has reviewed that applications of MEA differs across various EU countries, while considering different indications of the same medicines. Financial based agreements are found more common when compared with performance-based agreements. Other than Italy performance-based agreements are not commonly applied in other EU countries. Netherlands is another country where performance-based agreements are being used however they were abandoned as they don't work with the market forces. In England discounts and free stocks are used. Also, evidence development is of major focus in Netherlands and Sweden. Belgium applies a mix of approaches used in England, Sweden and Netherlands. Apparently, reasons for introduction of various MEAs appear same across countries.

A study by Pauwels et al; [56] has observed variations for applications of MEAs across counties and across different indications of same medicines, These variations in implementation of MEAs are probably related to

different health care systems. Other assumptions linked to these MEAs variations are level of uncertainty, capacity to pay, relative cost-effectiveness and their impact on the overall budget. Further research is required to explore the reasons for variations in implementation of MEAs across countries. [56] [57]

In a survey by Morgan et al; [58] for payers in North America, Europe, and Australasia, respondents were of the view that confidential discounts were most prevailing , and are normally used for specialty medicines. This survey also identified that the little similarity was observed between the list prices and the real price payers pay to the manufacturers. [58]

Dunlop et al;[59] conducted a survey of payers in EU, using the information to derive policy implications for future innovative pricing agreement(also known as MEAs) proposals. Survey participants were optimistic for innovative pricing agreements and foresee an increase in their use across EU. However, it is not expected that it will follow a one size fits all model as these agreements needs to be adopted to the varying needs of different therapeutic areas, varying needs of healthcare systems and also to the varying payers' expectations. Further research is needed in regards to performing a survey with a larger number participants and across other geographies by investigating payer preferences in more detail .[59]

Patient access schemes are an arrangement between UK department of health and maufacturers to endorse high cost medicines for usage at NHS level. According to Jarosławski & Toumi, [60] these schemes are driven by NICE and address uncertainty around the cost effectiveness of high cost medicines. In the UK, these schemes are of financial nature and instead of lowering the list prices , concessions and refunds are agreed. However, the study does not confirm manufacturers motivations for these arrangements. It is difficult to understand PAS schemes in the context of reference pricing (because of the confidential discounts, rebates negotiated with the payors in PAS schemes), hence there is a need for a process which is transparent and can aid fair assessment of these schemes. [60]

In 2010, England had introduced Cancer drug fund to support NHS to buy drugs which were not approved by NICE. According to Aggarwal et al; [61], there is no indication that substantial funds which were allocated to this program has brought significant benefit to patients. Number of changes have been made to this program and in July 2016 this has been renamed as managed access fund.[61]

Co-payments are expenses patients have to bear for a covered health service. According to Alam et al; [52], elimination of co-payments in Wales had increased the dispensing rates but this impact on dispensing rates is not significant.[52]When compared with prior studies, the magnitude of drops in co-payments looks very similar. [15]

Stakeholders involvement/ views on Reimbursement Process

It is important to understand the opinions and prefrences of the various members of funding bodies particularly decision making bodies. There is variability in views of the different members depending upon their roles and responsibilities within these organization.[62]

Due to scarce resources, health care rationing is the need of time and this needs an organized approach while allocating funds. Therefore in situations where it is hard to reach an agreement the stakeholders should proactively seek views of members e.g general pubic, which are noramally not included in decision process. [63].

Opinions and views of general public are vital in process of priority setting. A study by Bourke et al; [14] indicates that general public does not value funding recommendations for orphan drugs at higher threshold of cost effectiveness. These findings have consequences regarding the suitability of current policies of recommeding the orphan drugs at a very high threshhold, partcularly considering the rise in numbers of people with these diseases and the cost of orphan drugs [14].

A study by Cavazza & Jommi [64] investigating stakeholders' involvement by Health Technology Assessment Organisations in France, Spain, England and Wales, Germany, Sweden, and The Netherlands, indicates that the NICE involves all relevant stakeholders in an HTA process and in the subsequent decisions making process. Industry has a voting right in all appraisals in the UK. All stakeholders are deeply involved in the decision-making process, which is reflective of UK administration style. This study concludes that due to the variations in administrative styles and priorities of various health care systems in different countries, stakeholders' engagement approach in one country is not easy to be implemented in another country. [64]

Another study by Rosenberg-Yunger et al;[65] has reviewed stakeholders' involvement in the priority setting and the appeals processes of six drugs across five drug reimbursement recommendation committees in Australia, Canada, England Israel, Wales, and the USA. This study revealed that the stakeholders who were frequently engaged in the process were health professionals, academics and the general public. Industry representation was found to vary across different committees. Pharmaceuticals manufacturers were able to formally appeal decisions in all studied countries, except Israel and the USA. There is variability in types of stakeholders involved, degree of involvement in overall appraisal, and also in the revisions and appeals process. The study identified a number of stakeholders already engaged, as well as stakeholders whom they believed must be involved. It was understood that the engagement of all relevant stakeholder would lead to a just and authentic process for the reimbursement of new drugs.[65]

IV. Discussion

Access to Medicines in UK and Europe

Studies included in this review indicate variability in access to medicines across EU countries including the UK. While EU countries show a great promise with regards to fulfilling the WHO goals of Universal health coverage, people are still missing out on key medicines [5]. Variability in access to medicines is driven by the time to entry of new medicines in individual European countries. Time to entry of medicines is positively impacted by shorter intervals from licensing to submission for reimbursement, presence of a local sales representative, prelaunch evidence of added clinical value and size of the market. The study focuses on early access but do not comment on whether there are longer term differences [21]. Access to medicines is variable across different categories of medicines including ones for rare diseases and is impacted by high costs, poor efficacy/safety evidence, and societal preference for funding of orphan drugs. [22]

The UK has been found to fund relatively higher number of medicines, newest medicines and innovative medicines in comparison to US, Australia and the New Zealand. However, the UK is relatively slow at reimbursing new medicines when compared with other EU countries and there is also variability in access to different types of medicines across the UK [11].When EU countries including the UK were compared with Japan, the Japan seems to have relatively higher insurance coverage and greater access to more number of medicines[20]. The patients in Wales are found to have relatively faster access to new medicines over those in the England. [12] For the UK patients to have best healthcare, though there is a need to invest further, prioritization is also needed to ensure timely access to new medicines. [11]

Health Technology Assessment (HTA) in UK and Europe

This review includes multiple studies which explore various aspects of health technology assessments. Analysis of HTA decisions in context of their impact on patient access is of great importance. While one study in this review indicates that restrictive HTA decisions have financial impact on NHS [26], another study confirms that negative and restrictive HTA decisions do not essentially impact prescription rate and cost [17]. This could be due to lack of adherence with HTA recommendations at the level of prescribers or it could also be attributed to non alignment of purpose of decisions makers in HTA bodies and local health service. [27][25]

National Institute for Health and Clinical Excellence (NICE) conducts technology appraisals for new and existing medicines. NICE generally only reviews medicines referred to it by Ministers (unlike with the SMC, which appraises all new medicines when they receive a license). The NHS in England and Wales is obliged to adhere to the NICE guidance. The Department of Health [DH], Social Services and Public Safety in Northern Ireland has links with the NICE and it reviews any guidance issued by the NICE and decides whether it is applicable to Northern Ireland.[9] DH, in Northern Ireland also takes in to account SMC's decisions. The Department of Health in the Northern Ireland conducts a review of products on case by case basis but does not technically carry out a HTA even in the absence of NICE or SMC guidance [6].In Sep 2018, the Department of health in the Northern Ireland announced plans to improve access to innovative new medicines for cancers and other diseases. New plan introduces changes to ensure patients in Northern Ireland have same level of access to cancer drugs as their counterparts in the other UK regions.[66]All Wales Medicines Strategy Group (AWMSG) follows The National Institute for Health and Care Excellence (NICE) guidance if available. However, for the medicines where NICE guidance is not available, AWMSG assesses the medicines and its decisions are superseded if NICE guidance becomes available anytime later. [12] Analysis of All Wales Medicines Strategy Group (AWMSG) HTA decisions included in this review could not identify an independent factor influencing the recommendations. [25]

Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees (ADTCs) across Scotland about the status of all newly licensed medicines, all new formulations of existing medicines and also regarding the new indications for established products (licensed from January 2002). SMC aims to issue advice to NHS Scotland on all newly licensed medicines as soon as it's practical after the product launch.[67] In Scotland, the result of cost effectiveness analyses is important factor in SMC reimbursement recommendations. [24] When compared with the Poland, Scotland SMC issues fewer negative recommendations and Sottish HTA guidelines are more comprehensive as they provide more information to the

manufacturers for HTA submissions.[32]When compared with the France, Scotland recommends less medicines than the France. [33]

In countries which are relatively advanced in HTA implementation, the key aims of HTA are to improve quality of care, guaranteeing equal access, and the use of resources efficiently. Relatively less advanced countries often pursue the recommendations of other countries at advanced stage of implementation. These countries put more weight on the budget impact of new medicines and the use of HTA as a tool for cost estimation. [36] In England public guidance for health technology evaluation is available and the evaluations are based on the manufacturer submitted evidence. [34]

Review of the HTA practices,processes and policies in EU including the UK identify differences which are reflective of differences in priorities of decision makers, implementation process and framework at individual country levels. [30] HTA decisions comparison across the EU countries shows moderate to poor agreement. This difference could be related to the timing of the HTA assessments, status of medicines (Orphan vs non-Orphan), categories of medicines offering low value for money, difference in HTA processes, variations in how the submitted evidence advises the evaluation, difference in national preferences, regulatory structure and overall decision-making process [34] Each HTA body base their decisions using different evidence base. Differences in evidence resulted from differences in the consideration of indirect and mixed- treatment comparison data and differences in medical practice in each country. [35] HTA evaluation criteria in all countries are normally based on the effectiveness, safety, relative effectiveness, and economic data. [36]

In some EU countries including the UK, prices and access to a new medicine has to be justified by the health gain it delivers compared with the existing treatments, usually articulated in quality-adjusted life-years (QALYs) gained. In other countries e.g. France, the assessment of added value is based on an assessment of the clinical outcomes as compared with the existing treatments. The assessments of the value added by new medicines in England and France were found similar. However, approach followed in England is considered extra transparent and creates more political deliberation. Both approaches are appearing to converge, with England confidential price negotiations and France announcing newer requirement to estimate cost-effectiveness. [37]

In United Kingdom, overall appraisals outcomes (i.e. positive, negative or restrictive recommendations) across different HTA organizations are not fully aligned but found nearly similar. There is evidence which suggests that patients in Wales gain earlier access to medicines compared to patients in England [12] In comparison to Scottish Medicine Consortium (SMC), NICE recommendations are relatively more restrictive hence covering sub populations. Scottish Medicine Consortium base their evaluations on manufacturer submissions while NICE uses manufacturer as well as third-party assessments. [39]

HTA bodies analysed in this review share some similarities in decisions making process. Majority of HTA bodies focus on clinical efficacy and cost effectiveness. All have an explicit or implicit quality adjusted life year threshold. [40] Differences in HTA recommendations could be attributed to individual body's approach to risk perception, uncertainties surrounding a range of factors including cost-effectiveness, choice of comparator, clinical benefit, safety, trial design, and timing of submission.[40] It is also because of different priorities/likings

of HTA bodies, therapeutic area, levels of evidence, perceptions of value, tools used to address uncertainty, and the capacity and inclination and to implement risk sharing agreements, [7]. This also includes variability in the mandate of agencies, characteristics and decision-making process as well as the consequences of a negative decision for patient access[41]

The German FJC (Federal Joint Committee) is likely to apply more stringent criteria requirements in terms of comparative effectiveness than the NICE. [41]. It was observed that the higher proportion (95%) of orphan drug submissions were approved for reimbursement in the Netherlands, compared with relatively lower proportion (21%) in the Scotland. Moreover, cost-effectiveness or cost-utility analyses were included in majority of the submissions in Scotland when compared with the Netherlands.[42]

The UK & Spain share the same practice and only appraise carefully chosen medicines. There are more medicines assessed in Spain than by NICE as there are more HTA bodies in Spain and the processes in Spain are simpler. There are more refusals from NICE than by Spanish HTA bodies. While NICE uses cost-effectiveness thresholds in their appraisals resulted to a 'not recommended' decision in many cases; Spanish bodies are inclined to recommend more cancer drugs where better outcomes can be obtained. Spanish Committees take lesser time than the NICE, probably because of the relatively simpler appraisal process in Spain.[44]

The health economic evaluation is obligatory in most countries in the EU including the UK for reimbursement applications, but Germany has not largely followed it. [45],[46] Health economic evaluation generally use cost-effectiveness analysis and budget- impact analyses. The preferred outcome of cost- effectiveness analysis is quality-adjusted-life years. [46] However, critics have argued that the health economic evaluation is a rhetoric as it is found to have little impact to restrict access to expensive medicines[46]

The Policies for real world data (RWD) use vary across HTA agencies in the EU. Studies in this review reveals that RWD is being included more frequently in CEAs than REAs in the HTA evaluations. In some cases, RWD is only used for prevalence and/ or incidence, and in others for drug effectiveness and safety. To facilitate the use of RWD for HTA across Europe, more alignment of policies seems necessary. [47] [48]

This review confirms that in Europe, role of Comparative Effectiveness Research (CER) has increased in drug coverage decisions and, to some extent towards pricing decisions. While it contributes to evidence-based decision-making, it also helps in finding the medicines offer best value for money. [49] Analysis of Relative effectiveness assessments (REAs) of medicines for pricing or reimbursement decisions reveals that there is preference for clinically and patient outcomes related end points (Overall Survival (OS) and Quality of Life (QoL)) over surrogate end points. It was found that all of REAs include OS data, but this data is not robust at all times. It was found that 70% of the REAs include progression free survival (PFS)data. In 54% of REAs QoL data was included but it had little influence on the HTA decisions. [51]

Pricing

The prices in any country are typically determined either via regulatory approach or the market forces. The UK is an example of the country with a more formal regulatory approach for price setting as NICE use the cost

effectiveness analysis for newer medicines. In the United States, assessment of cost effectiveness is done by market forces instead of a structured approach. While value-based pricing is applied in both countries and it is driven by different mechanisms (regulatory vs market) it cannot be confirmed that different mechanisms lead to different outcomes.[52]

In year 2018 UK government has agreed a new five-year medicines pricing deal with the pharmaceutical industry to replace the nearly 60-year-old Pharmaceutical Price Regulation Scheme (PPRS). The new Voluntary Scheme for Branded Medicines Pricing and Access has been agreed in principle with the Association of the British Pharmaceutical Industry (ABPI) and has come into effect from 1 January 2019. The new scheme introduces an annual 2% cap on the growth of branded medicines sales to the NHS, while any overspend will be repaid by pharma companies as a refund based on the net sales. This is expected to bring £980 million savings to NHS. In return, the industry is expected to get "more and faster NICE appraisals for new medicines" – perhaps six months' sooner than at present. In principle, this will address pharmaceutical companies concerns about the UK's uptake of new drugs considered relatively slower than the other European countries.[68][69]

Risk-Sharing Agreements in UK and Europe

Managed entry agreements (MEAs) are arrangements agreed between the pharmaceuticals manufacturers and the organizations having authority to approve funding for the new medicines where clinical evidence and financial impact of the medicine is uncertain. This uncertainty constitue a risk and MEAs are introduced to help sharing this risk between pharmaceuticals manufactrers and payers.[56] Managed Entry Agreements (MEAs) are growing in numbers and it is expected that MEAs use will continue to expand in the future.[56] It is not expected that this will be a one size fits all model as these agreements needs to adopt to the varying needs of different therapy areas, healthcare system structures and payers' expectations. [59] With regards to type of agreement, financial based agreements are more common when compared with the performance-based agreements. Other than Italy, performance-based agreements are not commonly applied across other EU countries. In Netherlands performance-based agreements were used but have been given up due to their incapacity to work with market forces. In the UK, Patient access schemes which allow discounts and free doses are being used. Because of the confidential discounts, rebates are negotiated with the payors in PAS schemes and there is a need for a transparent and fair process which aid assessment of these schemes. [56] [48] Evidence development is of major focus in Netherlands and Sweden for these schemes. Belgium applies a mix of above-mentioned approaches. Reasons for introduction of various MEAs appear same across countries but it is not common that MEAs are implemented for the same medicines across different EU countries. In countries where MEAs are implemented for the same medicine are usually of different types. These variations in implementation of MEAs are related to different governance structure of the health system in these countries. Other assumptions linked to these MEAs variations are level of uncertainty, capacity to pay and the relative standing of cost-effectiveness and budget impact. [56] [57].

In 2010, England had introduced Cancer drug fund to support NHS to buy drugs which were not approved by the NICE. There is no indication that substantial funds which were allocated to this program has brought significant benefit to patients. In July 2016 after itroducing number of changes NICE has launched a revised programme amd renamed it as managed access fund. This provides access to drugs for up to 2 years after which resubmission

to NICE would be required. At re-submission, NICE will either approve the drug for standard funding or remove the recommendation for use.[61][70]

Co-Payments

To offset increasing cost of healthcare expeditures, many countries including the UK mandate co-payments for prescription medicines as a flat fee per item dispensed to patients. A unified approach to prescription co-payment has exsisted across all parts of the UK untill 2000 when the Welsh Government froze the co-payment and completely abolished it in April 2007. These co-payments could negatively influence the affordability and thus access to medicines, particularly in lower income patients. According to Alam et al; [15], elimination of co-payments in Wales had increased dispensing rates, however the impact was not found significant.[15]

Stakeholders' views on reimbursement process

There is variability in views of the different stakeholders depending upon their roles and responsibilities in individual organization.[62] This variability in views is reflective of diference in administrative styles and priorities in various healthcare systems[64]. Socially robust decisions which involve greater degree of stakeholders engagement are found more convenient to implement when compared to bureaucratic decisions. Therefore in situations where it is hard to reach an agreement, organizations should proactively seek views of members , for example general pubic, which are generally not included in the decision process. [63].

Future Research

Medicine licensing and reimbursement environment is continuously evolving and there are opportunities for learnings and collaborations among countries which are at different stages of advancement. There is a need to do further comparative studies to explore the status of access to medicines across all countries in the United Kingdom

Limitations

As per defined inclusion criteria studies only in English language were included. If anything was published in another language it has not been included. For papers included in this review publication bias has not been assessed. Depending on type and purpose of funding which cannot be necessarily assessed, bias could have led to publication or non-publication of the papers. Bias in terms of publication and outcome reporting bias may have led to publication or non-publication of articles depending on the nature or direction of the finding of which we cannot account for.

V. Conclusion

This review indicates variability in access to medicines across all countries in United Kingdom & EU and across different categories of medicines. Variability in access is driven by many factors which is reflective of differences in reimbursement and pricing process, mandates of agencies, characteristics and decision-making process, stakeholder's /societal preferences, differences in evidence requirements to support reimbursement, interpretation of submitted evidence, and the lack of adherence with reimbursement recommendations. In the United Kingdom NHS make decisions to reimburse medicines based on advice from health technology assessment bodies. In United

Kingdom, appraisal outcomes across different HTA organizations are not fully aligned but found nearly similar. There is a need to do further comparative studies to explore the status of access to medicines across all countries in the United Kingdom.

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