Pharmaceutical Care & Health Systems

Case Report Open Access

Initiatives among Authorities to Improve the Quality and Efficiency of Prescribing and the Implications

Godman B[1,2,3], Acurcio FA[4,5], Guerra Júnior AA[5], Alvarez-Madrazo S[2], Faridah Aryani MY[6], Bishop I[7], Campbell S[8], Eriksson I[9], Finlayson AE[10], Fürst J[11], Garuoliene K[12], Hussain S[13], Kalaba M[14], Jayathissa S[15], Abdol Malek AA[16], Małecka-Massalska T[17], Mansor Manan M[18], Martin A[19], Pedersen H[20], Sović Brkičić L[21], Smoleń A[22], Truter I[23], Wale J[24] and Gustafsson LL[1]

[1]*Division of Clinical Pharmacology, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden*
[2]*Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK*
[3]*National Institute for Science and Technology on Innovation on Neglected Diseases, Centre for Technological Development in Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil*
[4]*Medical College, Federal University of Minas Gerais (UFMG), Av. Alfredo Balena, 190, 7th floor, CEP 30130-100, Belo Horizonte, MG, Brazil*
[5]*Pharmacy College, Federal University of Minas Gerais (UFMG), Av. Antônio Carlos, 6627, sl 1048, CEP 31270-901, Belo Horizonte, MG, Brazil*
[6]*Pharmaceutical Services Division, Ministry of Health, Kuala Lumpur, Malaysia*
[7]*Public Health and Intelligence Business Unit, NHS National Services Scotland, Edinburgh, UK*
[8]*Centre for Primary Care, Institute of Population Health, University of Manchester, UK*
[9]*Public Healthcare Services Committee Administration, Stockholm County Council, Stockholm, Sweden*
[10]*Doll Fellow, Green-Templeton College, Oxford University and Academic Clinical Fellow, Nuffield Department of Primary Care Health Sciences, University of Oxford*
[11]*Health Insurance Institute, Ljubljana, Slovenia.*
[12]*Medicines Reimbursement Department, National Health Insurance Fund, Vilnius, Lithuania*
[13]*National Institute of Health, Islamabad, Pakistan*
[14]*Republic Fund for Health Insurance, Belgrade, Serbia*
[15]*Department of Medicine, Hutt Valley DHB, Lower Hutt, Wellington, New Zealand*
[16]*Hospital Tuanku Ja'afar, Seremban, Malaysia*
[17]*Physiology Department, Medical University of Lublin, Radziwillowska Street 11, 20-080 Lublin, Poland*
[18]*UiTM Puncak Alam, Selangor, Malaysia*
[19]*NHS North West Commissioning Support Unit, Salford, Manchester M6 5FW, UK*
[20]*Health Technologies and Pharmaceuticals, Division of Health Systems and Public Health, WHO Regional Office for Europe, Copenhagen, Denmark*
[21]*Croatian Health Insurance Fund, Branimirova 37, Zagreb, Croatia*
[22]*Department of Epidemiology, Medical University of Lublin, 1 Chodzki St, 20-093 Lublin, Poland*
[23]*Drug Utilization Research Unit (DURU), Department of Pharmacy, Nelson Mandela Metropolitan University (NMMU), Port Elizabeth, 6031, South Africa*
[24]*Independent consumer advocate, Victoria, Melbourne, Australia*

Abstract

Introduction: Medicines have made an appreciable contribution to improving patient care in recent years. However, European and other countries are increasingly struggling to fund new premium priced medicines. This has resulted in models to optimise their utilisation as well as multiple initiatives to improve the prescribing of established medicines including enhancing the use of low cost generics, improving adherence to prescribing guidance as well as access to medicines, ensuring adequate doses are prescribed and improving patient adherence rates especially in chronic asymptomatic conditions.

Objective: Review a range of demand-side initiatives in ambulatory care across different countries and their resultant effects to provide future direction.

Methodology: Principally a narrative review of case histories of published studies.

Results: Measures to encourage the prescribing of low cost generics versus originators and patented products in a class can release considerable resources without compromising care. However, there is no 'spill over' effect between classes. Consequently, multiple demand-side measures are needed to effect changes in physician prescribing habits. In addition, there are classes where there is caution, e.g. atypical antipsychotics. Activities surrounding the 'Wise List' in Stockholm healthcare region, including continuous medical education with resultant high prescribing adherence rates to a list of approximately 200 medicines, provides guidance to authorities where there are currently limited programmes to improve the quality of prescribing. Adequate dosing can be a concern necessitating strategies to assess current dosing levels to plan for the future including potential ways to address this. There are also concerns with adherence rates especially among patients with chronic asymptomatic diseases. This is resulting in activities by authorities to address this including adherence clinics.

Discussion: Multiple measures can enhance the quality and efficiency of prescribing, and authorities need to continually learn from each other to achieve desired results. The involvement of all key stakeholder groups including patients, pharmacists and physicians can enhance the rational use of medicines and enhance prescribing efficiency.

Keywords: Demand-side measures; Generics; PPIs; Renin-angiotensin inhibitor drugs; Statins; Dabigatran; Adherence; Guidelines; Dosing; Pharmaceutical care

Introduction

Medicines have made an appreciable contribution to improving health outcomes [1,2]. However, pharmaceutical expenditure is coming under increasing scrutiny worldwide [3,4] with expenditure rising by more than 50% in real terms during the past decade among OECD countries [5]. This growth has resulted in pharmaceutical expenditure now the largest, or equalling the largest, cost component in ambulatory care, and in some countries is up to 60% of total healthcare expenditure [4,6]. This scrutiny will continue with ever increasing pressure on

***Corresponding author:** Brian Godman, Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Tel: 00468 585 81068; E-mail: Brian.Godman@ki.se

Received August 06, 2014; **Accepted** August 25, 2014; **Published** September 02, 2014

Citation: Godman B, Acurcio FA, Guerra Júnior AA, Alvarez-Madrazo S, Faridah Aryani MY, et al. (2014) Initiatives among Authorities to Improve the Quality and Efficiency of Prescribing and the Implications. J Pharma Care Health Sys 1: 113. doi:10.4172/jpchs.1000113

available resources, caused by well defined factors including ageing populations, rising patient expectations and the continued launch of new premium priced technologies as single or combined entities [3,7-9].

European and other countries are increasingly struggling to fund new premium priced medicines due to resource issues [10-12]. If not addressed, this will grow commensurably with increasing prices of new biological drugs, which account for an appreciable number of new medicines in development [13]. These are typically priced between US$100,000 to US$400,000 (€74,000-296,000) per patient per year or more [7,14,15]. In addition, new treatments whilst effective could have an appreciable impact on overall drug expenditure as potentially seen with new treatments for patients with hepatitis C virus [16]. Measures to optimise the use of new medicines include models to improve their managed entry, starting pre-launch and continuing post-launch [12,17]. Initiatives also include an increase in managed entry agreements to enhance the value of new medicines, and hence their potential funding, together with the evaluation of data from registries and databases post-launch to assess utilisation patterns as well as the effectiveness and safety of new medicines in routine clinical care [9,18-25]. These activities will continue. However, care is needed with managed entry agreements given current concerns with the level of administration, apart from potentially straight discounts, the need to engage qualified unbiased professionals including physicians when appraising them as well as necessary information technology sophistication for any proposed outcome-based scheme [12,18,26].

Multiple demand-side reforms and initiatives are also being instigated by health authorities, physicians and pharmacists across countries to improve the quality and efficiency of prescribing with established medicines. These include measures to enhance the use of generics versus originators through for instance encouraging voluntary International Non-proprietary name (INN) prescribing; alternatively, instigating compulsory INN prescribing [10,27,28,30] or compulsory generic substitution [31,33]. Alongside this, measures to encourage the prescribing of generics versus patented (single-sourced) products in a class where all the products in the class are seen as essentially therapeutically similar at appropriate doses, e.g. the proton pump inhibitors (PPIs), statins and the renin-angiotensin inhibitor drugs, which include both the angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [29,34-43].

Such multiple demand-side measures can result in appreciable savings especially when coupled with low prices of generics, which can be as low as 2-10% of pre-patent loss prices in some countries [29,32,36,44-46] The savings from increasing the use of generics can help fund new medicines, increased drug volumes, increased patient access or a mixture of these. This is important given the continual pressure on resources coupled with annual global sales of pharmaceutical products losing their patents between 2008 and 2013 estimated at US$50 to 100 billion (€35-70 billion). This rises to US$255 billion (€190 billion) between 2011 and 2016 [47-49].

Other potential measures to improve the quality and efficiency of prescribing include initiatives to enhance physician involvement in continuous medical education programmes including educational initiatives around a selected list of well proven medicines, which are typically available as generics [32,50]. Patient care is enhanced through increased physician familiarity with the medicines they prescribe [50,51], potentially reducing adverse drug reactions (ADRs) as well as drug interactions. Average treatment costs for a single ADR in Germany were estimated at approximately €2250, equating to €434million per year [52], with the cost of emergency related admissions in the UK due to ADRs estimated at GB£2billion (€2.4billion) annually [53]. In the US, the cost of drug-related morbidity and mortality exceeded US$177billion (€130billion) alone in 2000 [54]. Pharmacists working with medicine management teams within health authorities can also play a role to improve care through academic detailing activities, working in pharmacotherapeutic teams including quality circles as well as part of therapeutic switching programmes in agreed patient populations [36,45,55-58].

Prescribing adequate doses and routinely monitoring patient outcomes is the basis of effective and safe drug therapy [50,51,59]. Published studies have shown that regular monitoring of International Normalisation Ratio (INR) levels with warfarin is variable across countries[60], which needs to be addressed. Published studies have also shown that good control of blood pressure in patients with hypertension and type 2 diabetes is essential to achieve a clinically important reduction in the risk of death and complications related to diabetes, including progression of diabetic retinopathy and deterioration in visual acuity [61]. However, regular monitoring of blood pressure is variable across countries. The same is also true with the prescribing of statins in patients with coronary vascular disease, with published studies showing substantial variation in the dosing of simvastatin for secondary prevention despite guidelines advocating 40 mg simvastatin [27,38,39]. Perreault and colleagues showed that good adherence to statins in patients with primary prevention was associated with a risk reduction of 18% compared with <20% for the remainder [62]. However, adherence can be low in patients with asymptomatic chronic diseases [63,64], e.g. Cramer and colleagues found that only 59% of patients took their medication for the treatment of diabetes, hypertension and dyslipidaemia for more than 80% of their days 'on therapy' in a year [65]. Medication adherence refers to the act of continuing the treatment for the prescribed duration, which is different to compliance as this typically refers to the degree or extent of conformity to the recommendations about day-to-day treatment with respect to the timing, dosage, and frequency [66]. Findings such as these resulted in blood pressure and lipid level targets in patients with diabetes, hypertension and cardiovascular disease included in UK quality standards (QoF) [28,29,44,67,68]. In addition, introduction of medication adherence clinics by health authorities, e.g. Malaysia [69]. These issues need to be addressed to improve morbidity and mortality especially in patients with chronic non-communicable diseases (NCDs).

In view of the growing pressure on resources, health authorities need to continue learning from each other regarding potential additional measures they could consider to further improve the quality and efficiency of their prescribing. As a result, help achieve optimal pharmaceutical care [70]. The principal objective of this paper is to review a range of demand-side initiatives in ambulatory care across different countries and their resultant effects to provide future direction. We hope some of these initiatives will be particularly relevant to countries struggling to provide universal access in the face of growing prevalence of non-communicable diseases.

Methods

This is principally a narrative review of case histories based on publications or internal health authority documents known to the multiple co-authors. Alternatively, unpublished studies the authors have been involved with. This is not a systematic review of published papers as review papers appraising the many factors influencing

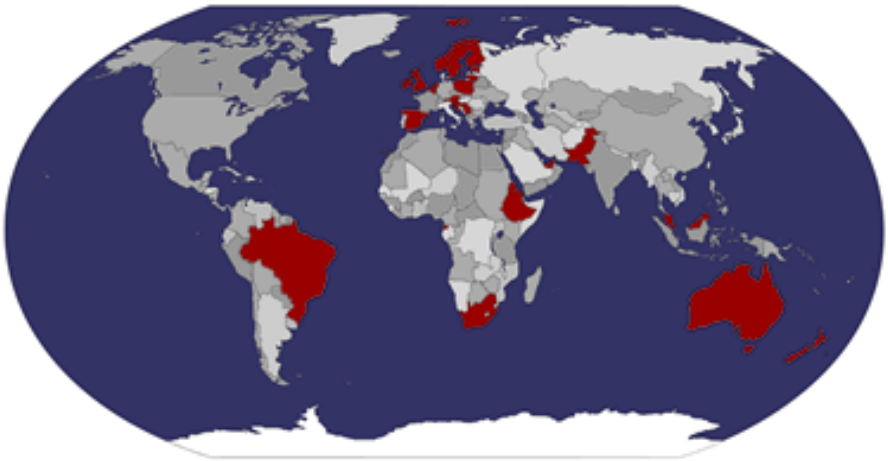

Figure 1: Countries involved in the case histories (red).

- Anti-epileptic drugs
  - Carbamazepine - it may be prudent to avoid changing the formulation particularly modified release preparations
  - Phenytoin - there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients
  - Phenobarbital, primidone - Commission on Human Medicines (CHM) advises physicians that patients should be maintained on the same brand*
- Asthma treatments
  - Theophylline modified release preparations – typically not seen as interchangeable with Council of the Royal Pharmaceutical Society advising that the brand name be specified on prescriptions
  - Beclometasone dipropionate CFC-free inhalers as well as inhaler dry powder devices generally where administration approaches differ with different instructions impacting on patient familiarity
- Calcium antagonists - modified release preparations, e.g. diltiazem longer acting and nifedipine modified release preparations, are typically seen as not interchangeable
- Immunosuppressants - Cyclosporin – concerns with different bioavailability between different preparations
- Miscellaneous
  - Amphotericin intravenous - prescribe by brand name as doses depend on the formulation
  - Lithium – concerns with differences in bioavailability between different formulations
  - Morphine sulphate slow release tablets – doses prescribed should be reviewed if the brand is change due to different release patterns between the different formulations
  - Transdermal formulations of fentanyl - there may be important differences in formulations between the different brands leading to differences in release characteristics

*CHM advice can be found at http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON336716

Box 1: Examples from the UK where there have been concerns with INN prescribing and the possible rationale based on recommendations in the British National Formulary (BNF), the Council of the Royal Pharmaceutical Society and the Medicines and Healthcare Products Regulatory Agency. (adapted from Ferner et al. [84] and Duerden et al. [85].

pharmaceutical expenditure, potential initiatives to improve pharmaceutical care as well as potential approaches to favourably influence physician prescribing, including enhancing the utilisation of generics, have already been published by the authors and others [34,57,70-77]. There have also been comprehensive publications to improve the quality and teaching of clinical pharmacology to enhance subsequent patient care [78].

We also did not critique the quality of any of the papers quoted in the case histories as a number of these involved the co-authors.

However, we believe our approach is valid given the extensive and wide experience of the co-authors across countries as well as their publications on relevant subjects. This applied approach has been used in other publications aimed at providing guidance to health authorities including quality indicators for new medicines [4,26,34,49,73,77,79,80].

Results

The case histories across multiple countries (Figure 1) are collated as four different categories outlined in the introduction. This includes measures to enhance the prescribing of low cost generics versus originators or patented (single-sourced) products in a class, measures to improve adherence to prescribing guidance, measures to address concerns with adequate dosing and access to medicines as well as measures to improve adherence to medicines.

Measures to enhance prescribing efficiency through increasing use of generics

Prescribing efficiency in this situation refers to similar patient outcomes between different treatment approaches at lower expenditure.

Encouraging the utilisation of generics versus originators: Scotland has introduced a range of measures and initiatives over the years to encourage INN prescribing. Activities start in medical school to educate students with the INN name of medicines, and continue into ambulatory care through education, monitoring and feedback as well as prescribing support systems [29,44]. This resulted in generics accounting for 98% to 99% of the total utilisation of medicines across a range of classes, enhanced by strict bioequivalence criteria, releasing considerable resources [29,44]. Health authorities have also successfully instigated pragmatic measures to enhance the prescribing of generics even when these are different salts to the originator with fewer indications, provided bioequivalence has been demonstrated. This was the case with generic clopidogrel when it became available [81].

Patient care is not compromised by such initiatives with published studies demonstrating similar outcomes between generics and originators to treat patients with cardiovascular diseases. This has even applied to medicines with narrow therapeutic indexes [82]. There were

similar findings for medicines to treat epilepsy [83], however, there are some concerns with INN prescribing of some of these medicines-Box 1 [84,85].

It is believed INN prescribing should be encouraged as this can reduce confusion if patients are dispensed different branded generics with different names on different occasions. This can happen in Sweden with monthly auctions for multiple sourced products now taking place. The company winning the auction, through offering the lowest price and capacity to supply the Swedish market, is guaranteed an appreciable proportion of dispensed prescriptions for that particular molecule the following month [32,34,49]. This may cause confusion to patients if they are dispensed different branded generics on different occasions and do not receive adequate information about their medicines from dispensers [32,86], potentially leading to either duplication of medicines; alternatively, patients not taking their prescribed treatments as directed. As a result, not gaining the most benefit from their prescribed treatment [87]. These scenarios are exacerbated if dispensers lack training on how to handle concerns with substitution and/ or do not receive adequate payment for providing relevant information to patients, potentially limiting their time with them [45,86]. INN prescribing, apart from a limited number of well-known situations (Box 1), is one way to address this as demonstrated in the UK [44].

However, such initiatives need to be carefully thought through before instigation to achieve the desired outcomes as illustrated by the experiences seen in the Health Authority of Abu Dhabi (HAAD). HAAD recently mandated INN prescribing apart from a limited number of exceptions similar to Box 1 [30,34]. This initiative combined with a comprehensive Generic Drug Policy (August 2009) sought to increase generic utilisation. However:

- Pharmacists were fully reimbursed for dispensing any molecule and received bonuses from manufacturers to preferentially dispense their product (originator or branded generic)
- Originator manufacturers did not have to lower their prices for reimbursement following generic availability, and patients did not have to pay the price difference for a more expensive molecule than the current lowest priced molecule
- Currently limited demand-side measures encouraging physicians to preferentially prescribe a generic versus a patented (single-sourced) product, e.g. a generic versus a patented PPI

As a result among the PPIs and statins, which were the two highest expenditure classes, utilisation of patented products grew following these various measures increasing overall costs [30]. HAAD is now considering a number of additional measures to address the situation, providing guidance to other countries of the need to fully think through potential future measures and initiatives before instigation.

Encouraging the utilisation of generics versus patented products in a class

PPIs and statins: Multiple demand-side measures in the Netherlands encouraging the prescribing of generics, coupled with low prices of generic PPIs and statins at 2% of originator pre-patent loss prices, resulted in reimbursed expenditure for the PPIs and statins falling by 58% and 14% respectively in 2010 Vs. 2000 despite a 3 and 3.8 fold increase in respective utilisation [36].

In Scotland, multiple demand-side measures coupled with low prices for generic PPIs and statins at 3% to 9% of pre-patent loss prices, resulted in reimbursed expenditure for the PPIs in 2010 56% below 2001 levels despite a 3 fold increase in utilisation. Expenditure on the PPIs was estimated to be GB£159million (€200million) greater in 2010 for a 5.2 million population without such measures [27]. Similarly, reimbursed expenditure for the statins in 2010 was only 7% above 2001 levels despite a 6.2 fold increase in utilisation [27]. Again, it was estimated that statin expenditure would have been GB£290million (€364 million) greater in 2010 without such measures.

Multiple demand-side measures in Sweden encouraging the prescribing of low cost generics at between 4% to 10% of pre-patent loss prices [32] resulted in expenditure/1000 inhabitants/ year in 2007 for both the PPIs and statins at less than one tenth of that seen in the Republic of Ireland with their limited demand-side measures [46]. There was though greater morbidity among the selected population in Ireland [46]. Others have suggested different findings with increased prescribing of patented (single-sourced) products following the availability of generics [88]. However, the author aggregated countries with both extensive and limited demand-side measures, which may have impacted on the findings [88].

Patient care is not compromised with all PPIs and statins seen as essentially therapeutically similar at appropriate doses and there have been examples of successful therapeutic switching programmes between the statins [28,37,38,40,43,89].

Renin-angiotensin inhibitor drugs

ACEIs Vs. ARBs: Multiple demand side measures introduced in Scotland including guidelines, rigorous Drug and Therapeutic Committees (DTCs), academic detailing, benchmarking, prescribing targets and financial incentives, limited the prescribing of patented (single-sourced) ARBs versus generic ACEIs. As a result, the utilisation of ARBs was only 19% of total renin-angiotensin inhibitors in 2007 (DDD basis). This compared with Portugal with few demand-side measures to combat the marketing activities of patented ARB manufacturers. ARBs subsequently accounted for 44% of total renin-angiotensin inhibitors in Portugal in 2007 [29]. The combination of multiple demand-side measures in Scotland coupled with low cost generic ACEIs, e.g. generic enalapril and lisinopril were 88% below pre-patent loss prices in Scotland in 2007, stabilised reimbursed expenditure on renin-angiotensin inhibitor drugs between 2001 and 2007. This was despite a 159% increase in prescribed volumes. This compared with Portugal where reimbursed expenditure grew steadily, 41% higher in 2007 than 2001, with volumes only increasing by 72% [29].

Patient care is not compromised with ACEIs and ARBs seen as having similar effectiveness at appropriate doses, prospective clinical studies showing coughing only occurred in approximately 10% of patients prescribed ACEIs and only 2% to 3% of patients in ACEI clinical trials discontinued their treatment due to coughing [29]

Generic Vs. patented ARBs: A recent Cochrane review concluded all ARBs had a statistically equivalent effect on lowering blood pressure, which was endorsed by the National Institute for Health and Care Excellence (NICE) in the UK stating that patients with hypertension can be started on either an ACEI or a low cost ARB [41,90-92]. Alongside this, there had been no head to head trials showing any difference in effectiveness between the various ARBs to treat patients with heart failure, although higher doses are typically needed to manage heart

- **Education**, e.g. support for professional initiatives including continuous medical education, distribution of printed guidelines and guidance including the 'Wise List' in Stockholm (below); academic detailing and the monitoring of prescribing against agreed guidance
  - Changes in guidance, guidelines, and formularies to recommend losartan first line for the management of hypertension or heart failure when an ARB is indicated
  - Academic detailing endorsing losartan as the ARB of choice
  - Monitoring/ benchmarking the prescribing habits of physicians against colleagues and against agreed guidance on a monthly basis and feeding the results back to preferentially encourage the prescribing of losartan
- **Engineering**, e.g. organizational or managerial intervention, including prescribing and quality targets
  - Prescribing targets, e.g. % losartan as a % of all ARBs (DDD based)
  - Active therapeutic switching programmes among some counties to switch patients on other ARBs to losartan
- **Economics**, e.g. financial incentives to physicians and patients including devolved budgets to physicians combined with financial incentives and additional co-payments for a more expensive drug than the current reimbursed drug (molecule or class)
  - Devolution of budgets to physicians combined with financial rewards for staying within budget
  - Revision of physician or practice based financial incentives to now include the prescribing of losartan versus other ARBs
- **Enforcement**, e.g. regulations including those enforced by law such as compulsory generic substitution and prescribing restrictions
  - There were no national prescribing restrictions for patented ARBs versus generic losartan
  - However, the restrictions limiting the prescribing of ARBs to second line still remained in place

Box 2: Multiple measures to enhance the prescribing of losartan in Sweden once generics became available collated under the 4Es [32,50,92,94-96].

Months	-16	-14	-12	-10	-8	-6	-4	-2	0	2	4	6	8	10	12	14	16
% Losartan	26	26	26	27	27	27	27	27	27	30	30	33	34	35	38	38	40
% other ARBs	74	74	74	73	73	73	73	73	73	70	70	67	66	65	62	62	60

Table 1: % losartan and other ARBs vs. total ARBs (DDD basis) in the months pre- and post generic losartan (Month 0) in Sweden (Month 0 – March 2010) [92].

Education
- Educating physicians that all ARBs are similarly clinically effective as part of a programme of meetings between the Medicines Management Team and all GP practices before any patient switching to introduce the prescribing incentive scheme, explain the programme, gain agreement and deal with any clinical issues that may arise
- Continued educational input to ensure continued high INN prescribing of losartan
- GPs subsequently informed patients why the switch had taken place to reduce potential confusion. Relevant community pharmacists were also informed about the campaign to enlist their help with reassuring patients at the time of dispensing to address any additional concerns and reduce possible patient confusion if this was required

Engineering
- Generic losartan included in prescribing targets for ARBs - target was that 85% of all renin-angiotensin inhibitor drug items prescribed were either an ACEI or losartan
- Instigation of therapeutic switching programmes for patients with hypertension currently prescribed other ARBs than losartan. This was undertaken by pharmacists and pharmacy technicians under Standard Operating Procedures (SOPs) agreed by the NHS Bury Medicines Management sub-group
- Under the SOPs, Medicine Management technicians undertook searches of GP clinical systems to identify potential candidates for therapeutic switching. GPs agreed to substitute losartan at their next prescription.
- Where potential concerns were identified in patients' medical histories, these were first discussed with medication review pharmacists in the Medicines Management group before any subsequent decision was taken
- All decisions to change were the ultimate responsibility of each GP. They were given a list of patients identified for potential switching by the technicians. They subsequently signed the list if approved; alternatively removed the patient from the list if concerns. Patients were recalled after 2 to 3 months and switched back to their original ARB if their BP was not controlled. Subsequently monitored regularly as part of the Quality and Outcome Framework initiative

Economics
- Devolved drug budgets taking account of generic losartan
- 15% of prescribing incentive monies (overall up to GB£0.90/ patient) to GP practices for meeting their prescribing targets for ACEIs and generic losartan
- 20% of the prescribing incentive scheme allocated to practices for coming within their indicative prescribing amount (generic losartan would contribute to this)

Enforcement
- Not applicable

Box 3: Multiple demand-side activities undertaken in NHS Bury to enhance the prescribing of generic losartan broken down by the 4Es (Adapted from reference [45].

failure compared with hypertension [45]. In addition, a recent cohort study demonstrated that in patients with heart failure, higher doses of losartan (100 mg/ day) were not associated with increased mortality compared with candesartan, which is different for lower doses [93]. Lastly, there was perceived to be no detrimental effect on compliance with switching patients between different ARBs as all were prescribed once a day and there were no apparent issues with possibly different excipients between different generic losartan preparations [45]. As a result, care should not be compromised through encouraging the preferential prescribing of generic versus patented (single-sourced) ARBs at appropriate doses [41].

Multiple measures were successfully introduced in Sweden as well as one English primary care trust (NHS Bury) to improve ARB prescribing efficiency once generic losartan became available. Following the availability of generic losartan, the counties (regions) in Sweden instigated a number of measures to increase its prescribing. The various initiatives both nationally and regionally, collated under the 4Es – Education, Engineering, Economics and Enforcement [94], are described in Box 2.

These multiple demand-side measures (Box 2) significantly increased the prescribing of losartan following generics (Table 1) [92]. These initiatives, when combined with reduced prices for generic losartan at 10% of pre-patent loss prices, reduced total single ARB expenditure by 26% by the end of the study in Sweden despite a 16% increase in utilisation [92].

There were initially no specific demand-side measures in one primary care group in England (NHS Bury) to preferentially enhance the prescribing of generic losartan versus patented (single-sourced) ARBs once generic losartan became available [45]. However, this changed in March 2011 with the urgent need for this primary care group to save considerable resources in view of the current financial deficit. This led to a range of measures being instigated to enhance the prescribing of losartan in patients with hypertension versus patented ARBs. These have again been broken down by the 4Es [94]. Similar to Sweden (Box 2), these centred on therapeutic switching programmes (Box 3). These measures resulted in a significant increase in the prescribing of generic losartan (Table 2) [45].

Month	-5	-3	-1	0	1	3	5	7	M0	M1	M3	M5	M7
Losartan	1107	1206	1237	1288	1188	1229	1343	1181	1399	1307	1894	2805	3201
All other ARBs	3484	3867	3835	4021	3634	3610	3974	3376	3873	3403	3556	2430	1752
% losartan	24	24	24	24	25	25	25	26	27	28	35	54	65

Table 2: Utilisation of losartan versus other ARBs (DDD basis) in items dispensed and percentages in NHS Bury before and after generic losartan [45]
NB. Months (numerical) = before and after generic losartan in July 2010 (-5 to 7). M0 to M7 = months after the initiation of multiple measures (Box 3) to increase losartan utilisation. % losartan = % losartan items dispensed vs. all ARB items dispensed in that month.

A) Key Criteria for listing
- **Efficacy and safety** – based on available evidence preferably including data from RCTs
- **Pharmaceutical suitability** – formulations, strengths, and pharmacokinetic properties
- **Efficiency** – mainly based on comparative reimbursed prices and the overall drug budget impact
- **Experience** – mainly concerned with drug safety
- **Environmental aspects** – if drugs are considered similar based on available evidence and similarly priced, environmental considerations guide choices

B) Key questions posed when considering new medicines for potential listing
1. What was the main scientific question posed?
2. How was patient selection conducted and diagnoses, etc.?
3. What patients were included in the control groups and what type of study was conducted?
4. Was the study-double-blinded, single-blinded, etc.?
5. How was the randomisation conducted?
6. What about the pharmacokinetics?
7. What about concomitant medications, are these documented, valid, etc.?
8. Are the drug effects well defined, relevant, reproducible, etc.?
9. What about adverse events, are these well studied, described, etc.?
10. How appropriate was the statistical design and evaluation of the results?
11. What about the conclusions of the studies – were these adequate, doubtful, etc.?

Box 4: Key criteria and questions typically posed in Stockholm Metropolitan Health Care Region when reviewing existing and new medicines for inclusion in the 'Wise List' [32].

As seen in Table 2, there was no immediate change in the utilisation of losartan in NHS Bury following the availability of generics. This changed after multiple demand-side measures were instigated (Box 3) principally involving the medicines management team. Following these multiple measures, losartan utilisation increased significantly to 65% of all single ARB items dispensed by the end of the study Table 2 [45]. Reimbursed expenditure on total single ARBs was 59% below pre-generic levels (M0) by the study end, helped by a 92% reduction in expenditure/ item for losartan. Annual net savings from the programme were estimated at just under GB£290,000 (€365,000), over eight times the cost of implementation [45].

Patient care was not compromised with patients actively followed up by physicians. Similar findings have been seen with other therapeutic switching programmes for ARBs in the UK [40,41].

Atypical antipsychotics: It is recognised by psychiatrists, clinical pharmacologists, pharmacotherapeutic experts and health authorities that there are classes where it can be difficult to introduce demand-side measures to appreciably increase the prescribing of multiple sourced versus patented medicines in a class. This is seen with the atypical antipsychotics for treating schizophrenia and bipolar disease. Experts as well as national authorities suggest pharmacotherapeutic treatment should be tailored to individual patients in view of the differences in effectiveness and side-effects between individual patients [8,97].

A recent cross national study showed there was a consistent decrease in risperidone utilisation as a percentage of all selected atypical antipsychotics following the availability of oral generic risperidone among a number of European countries, with no specific demand-side measures to preferentially encourage the prescribing of risperidone [8]. There were similar findings in Austria and Spain (Catalonia) [8,97]. Consequently, health authorities need to wait until more atypical antipsychotic drugs become available as generics before they will see significant reductions in expenditure. This is already happening across Europe [8] .

Guidelines/ prescribing guidance by physician directed DTCs and other bodies

'Wise List' – Stockholm Healthcare Region

In Stockholm Metropolitan Healthcare Region, with a population of 2 million people, there has been a tradition to select evidence-based medicines recommendations for common diseases during the past five decades directed by a high degree of involvement of prescribing physicians and respected pharmacotherapeutic experts and clinical pharmacologists [32]. The long term strategy has been to advocate that "each recommended medicine should be of high value to the patient" [50,51].

Since 2000, approximately 200 medicines have been selected for common diseases seen in ambulatory care including primary and outpatient care [50]. The recommended medicines are selected based on strict criteria including efficacy, safety and cost-effectiveness (Box 4), with each recommended medicine typically available for a minimum of two years on the Swedish market before consideration. Key questions are also asked when new medicines are being considered for potential inclusion in the formulary (Box 4). Since 2000, the list has been called the 'Wise List' with several different editions available including one for patients and one for the public. The 'Wise List' is updated yearly [50].

Respected specialists, working jointly with clinical pharmacologists, pharmacists and general practitioners in over 20 expert groups, suggest which medicines should be selected and included in the list [32,50]. The suggestions are approved by the DTC, with all approved suggestions subsequently collated into the 'Wise List' for that year, and widely communicated and disseminated [50,51].

Adherence to the voluntary 'Wise List' has increased during the past 10 years, enhanced by physician trust in the List, reaching 87% of all prescriptions in primary care in 2009 [50]. An essential step to assure high adherence has been to provide all prescribers with easy-to-use tools to compare their prescribing and adherence with each other,

Figure 2: Example of educational handouts in Minas Gerais as part of the academic detailing programme (Reproduced with kind permission of the State of Minas Gerais)

and between different healthcare settings, as well as provide prescribing guidance in an easy-to-use format [32,50]. This is seen as critical to the successful utilisation of the 'Wise List' in prescribing activities.

Separate studies have demonstrated that care is not compromised with adherence to the 'Wise List' recommendations, which typically include generic versus patented medicines in a class [98]. Overall, an annual increase in adherence by 1% in primary care in Stockholm is equivalent to €0.47 lower cost/prescription item [96]. This corresponds to annual additional savings in primary care in Stockholm healthcare region of €4 million or more, with the savings accelerating over time. This is in addition to improving patient care through physicians increasing their prescribing of medicines with proven outcomes as opposed to new medicines with as yet unknown long term benefits [12]. Adverse drug reactions and potential drug interactions are also reduced by the development and instigation of an alert system (SFINX) as part of the comprehensive approach decision support system for physicians within Stockholm healthcare region [99,100]. SFINX is also utilised throughout Sweden and other countries, e.g. Finland [99].

Guidelines for Alzheimer's disease and their implementation

As mentioned, educational outreach visits (academic detailing) have been shown to improve prescribing practices of healthcare professionals including the incorporation of clinical guidelines into clinical practice, although the results can be variable [57,58,101-103].

This activity has been incorporated into current demand-side measures in the State of Minas Gerais, Brazil. For certain medicines to be reimbursed in Minas Gerais, which include high cost and speciality medicines, physicians must follow agreed prescribing guidelines. Patients must pay 100% of the cost of the medicines if physicians do not meet the agreed prescribing criteria; alternatively physicians fail to complete the forms correctly. Educational activities are subsequently undertaken where pertinent to help improve physician adherence to agreed guidelines and reduce the potential for patient co-payments. The state of Minas Gerais believes this approach encourages the appropriate prescribing of medicines to patient groups where they provide the greatest benefit and value.

Recently, guidelines have been developed to improve the management of patients with Alzheimer's Disease in Minas Gerais. This is because dementia disorders are seen as the most common disease among the elderly in Brazil, reducing their social and occupational activities. Specific forms were designed for physicians to request

funding for the cholinesterase inhibitors, i.e. donezepil, galantamine or rivastigmine, based on the agreed guideline of care.

An analysis undertaken in 2012 showed that 12% of the treatment requests for Alzheimer's disease were returned or denied due to a lack of knowledge about the guidelines (Personal communication Guerra Junior AA). Consequently, activities have been ongoing to address this to improve the care of these patients. This includes academic detailing based on the clinical protocols and treatment guidelines for Alzheimer's Disease. This involves a six-step process including:

- **Step 1** - Information survey among physicians concerning their knowledge of the disease. Subsequently, a seminar about the disease with key facts
- **Step 2** - Study of clinical cases from both accepted and denied requests to gain practical knowledge
- **Step 3** - Elaboration of two educational handouts for the academic detailing programme: one focused on patients and caregivers, and the other focused on physicians or other health professionals with the principal aim of assisting the physicians in adequately completing their requests (Figure 2)
- **Step 4** - Training of pharmacy personnel for the educational outreach visits in a workshop
- **Step 5** - Academic detailing to orient prescribers. In addition, completing a report of the visit containing the prescriber`s impression of the process and their level of satisfaction
- **Step 6** - Evaluation of the study and the impact on improving guideline adherence

The study is still ongoing. If successful, this approach will be applied to other situations to efficiently improve the quality of care in Minas Gerais.

Antibiotic prescribing and dispensing in Serbia

There has been high antibiotic consumption in Serbia, with antibiotic consumption enhanced by self-purchasing in pharmacies. This self-purchasing increased antibiotic utilisation by 115% to 128% in recent years compared with reimbursed utilisation (via The Republic of Serbia Health Insurance Fund database). This resulted in Serbia having the third highest utilization for cephalosporins in 2007 among European countries, highest for penicillins, second highest for macrolides, and third highest for quinolones [104]. Consequently, reducing antibiotic consumption became a high priority among all national authorities to reduce resistance development and conserve resources. This is happening with greater enforcement of the law regarding self-purchasing following information and other campaigns, as well as the instigation of prescribing restrictions for second line antibiotics [104].

Concerns with the quality of prescribing

We are aware that there are countries where there are currently few activities among national or regional health authorities or professional medical groups to improve the quality and efficiency of prescribing in ambulatory care. The principal means of controlling pharmaceutical expenditure in a number of these countries has been through patient co-payments and reference pricing in a class (ATC Levels 3 to 5). This can potentially affect the resultant quality of care especially if prescribing choices are affected by co-payment issues [105-107].

Care can also potentially be affected if there is limited or no continuing physician professional development programmes to improve patient care through for instance improving aspects such as diagnosis and the dosing of medicines as well as knowledge of adverse drug reactions and drug interactions. The various initiatives in the Stockholm healthcare region surrounding DTCs and the 'Wise List', described earlier, is one way to help address this alongside for instance the development of quality indicators including those to improve pharmaceutical care [50,51,70,79,99]. However, care when introducing quality indicators in case of potential overload as well as unintended consequences [79].

Regulating pharmaceutical company marketing activities could also help improve the quality of prescribing, especially given some of the aggressive marketing and other activities that have taken place to influence physician prescribing [12,108-110]. The authorities in Croatia recently introduced strict controls regarding pharmaceutical company marketing activities. These included limiting contact between company representatives and physicians, as well as reporting all promotional expenses including any financial remuneration to physicians to the authorities to limit such activities [111]. Adherence is enhanced through a yearly financial deposit with Croatian Institute for Health Insurance (CHIF) with penalties for abuse, alongside potential delisting of products from the public reimbursement list and 'naming and shaming' offenders in public [111]. There have been similar activities in other countries [110].

We are also seeing health authorities working with physicians and other stakeholder groups pre-launch to improve the prescribing of new medicines post launch if there are concerns with patient safety when the new medicine is prescribed in a wider co-morbid population in routine clinical care. This happened with the recent introduction of dabigatran to prevent stroke and systemic embolism/clot formation in adult patients with non-valvular atrial fibrillation [12]. These concerns arose due to dabigatran's low mean oral bioavailability, considerable variation in plasma drug concentrations, and dependence on renal elimination of the active metabolite. Consequently, any accumulation of dabigatran in patients with reduced renal function will increase their risk of excessive bleeding, complicated by no known antidote and no commercially available assay to measure blood levels of dabigatran [12,17,112,113]. These concerns are enhanced by potentially more elderly patients in clinical practice than seen in the Phase III clinical studies increasing the risk of bleeding, which happened post-launch [12,113,114]. These concerns resulted in European health authorities and those in other countries instigating education and other activities in an attempt to improve the prescribing of dabigatran post-launch [9,12]. In New Zealand, extensive local educational initiatives by the Best Practice Advisory Centre (BPAC) in the Lower Hutt region as well as initiatives by local prescribers pre- and peri-launch resulted in no inappropriate prescribing of dabigatran according to patients' renal function post-launch [9]. Prescribing restrictions for dabigatran post-launch in Slovenia, e.g. only reimbursed if initiated by an internist or neurologist and prescribed according to agreed indications with patients entered onto databases and followed in a tertiary or secondary anticoagulation centre, also appeared to have enhanced the quality of prescribing post-launch [9] .

Adequate dosing of medicines and access to medicines

There appear to be under dosing of statins among a number of countries including Ireland, Netherlands, Norway, South Africa and the Stockholm healthcare region. An analysis of a cohort of patients aged ≥18 years in the Finnish Prescription Registry Finland prescribed statins for the first time showed that patients were typically initiated

with simvastatin (94% of the cohort) as 10 or 20 mg tablets. In addition, a considerable proportion of patients initiated on statin therapy with less potent doses remained at the initial dose after 1 year. This suggested potential under dosing was common, even among patients with a high CV risk [39]. The average dose of simvastatin for secondary prevention patients in Ireland was 22 mg in a recent study [32,115]. This was 20.4 mg in Stockholm with an appreciable proportion of patients dispensed only 10 mg of simvastatin[27,32]. There also appeared to be under dosing with simvastatin in the Netherlands with many patients prescribed starting doses at just over 15 mg (mean dose of 1.02 +/- 0.39 defined daily doses with the DDD for simvastatin at 15 mg during the study) [116].There was also variable dosing of statins among the different regions in Norway with under dosing in some regions. Patients in high statin consumption regions in Norway had the highest prescribed daily dose for simvastatin across all patients at 25.9 mg; similarly for atorvastatin at 21.9 mg. In addition, more users received tablets in the upper range of available strengths than seen in the low consuming regions in Norway [117].

In South Africa, a recent retrospective, cross-sectional pharmacoepidemiological study was conducted on claims data for 2011 of a medical insurance (medical aid) administrator provider. This included 4,805 patients (57% males) prescribed 38,373 hypolipidaemic agents, with all records extracted for analysis. Each medication record contained information on the age and gender of the patient, with a unique number to identify each patient, the date of the prescription as well as detailed information on the dispensed drug (name, package size, formulation, strength and quantity). Statin doses varied considerably, with the average prescribed daily dose of simvastatin for both men and women in 2011 at 23.7 mg, higher for atorvastatin averaging 20.9 mg [118] (Table 3).

This compares with substantial prescribing and dispensing of higher strength simvastatin (principally 40 mg simvastatin) and atorvastatin in England and Scotland following physician incentives under the Quality and Outcome Framework (QoF) [27,28,44].This was part of the initiative in the UK to improve the standard of care in patients treated in ambulatory care facilities [68]. As part of the QoF initiative, physicians received substantial payments for achieving lipid level targets in their patients with hypercholesterolemia [27,28,68]. This combined with national guidelines in Scotland advocating 40 mg simvastatin for secondary prevention including patients with diabetes [119,120] appreciably enhanced the prescribing of 40 mg (principally) and 80 mg (limited) simvastatin versus 10 and 20 mgs in recent years (Table 4).

Statin	Average PDD (mg)
Atorvastatin	20.9
Fluvastatin	57.3
Lovastatin	26.3
Pravastatin	25.4
Rosuvastatin	15.0
Simvastatin	23.7

Table 3: Prescribed Daily Dose (PDD) in mgs for patients in South Africa dispensed statins in 2011 [118].

There are though European countries where there has been limited utilisation of statins even without considerations of the doses prescribed [77]. This included Lithuania where in 2007 statin utilisation was just 0.8 DIDs (DDDs/ 1000 inhabitants per year - DIDs) compared with 93.6 in England and 114.74 in Scotland [77]. This difference can be explained by the considerable prescribing restrictions for statins in Lithuania at that time, i.e. statins were only reimbursed post AMI and only for 6 months otherwise 100% co-payment. In addition, the first prescription must be written by a cardiologist [77]. This compares with the encouragement in England and Scotland through the QoF targets, and statins fully reimbursed across all populations [27,28]. The restrictions have now eased in Lithuania. This resulted in the utilisation of statins increasing to 7.3 DIDs in 2012, higher at 12.9DIDs if patients paying 100% co-payment are included.

This is considerably different to the situation with renin-angiotensin inhibitor drugs in Lithuania. These are fully reimbursed in Lithuania without prescribing restrictions, which led to similar utilisation patterns in 2007 compared with other European countries (Table 5) [29,121].

Reducing the prevalence of non-communicable diseases (NCDs) is seen as a priority area across all countries given rising prevalence rates in recent years [122,123] This has resulted in the instigation of broad policy measures and communication programmes in Pakistan, including encouraging behavioural changes such as diet and exercise as well as screening for raised BP, dyslipidaemia and diabetes in high-risk groups. However, initial analysis suggests marked differences in the standard of care whether patients are treated in private versus public facilities. This included the extent of examinations and tests undertaken. Lipid lowering drugs including statins were the most prescribed drugs at 24% of all prescriptions. The majority of prescriptions though emanated from private physicians, with only a limited number from public providers. This was not helped by lipid lowering drugs typically being unavailable in most public health care facilities [122]. This situation needs to be urgently addressed to help reduce the morbidity and mortality of patients with diabetes across all sectors in Pakistan.

Improving adherence to medicines especially for chronic diseases

The next challenge facing health authorities is to enhance medication adherence. This is particularly a challenge in patients with chronic asymptomatic NCDs as demonstrated in a number of publications [63-65,124].

A survey on hypertensive patients in seven primary health clinics in Malaysia found that 46.6% of the patients were non-adherent to their medication regimes [125]. A similar study in diabetic patients found that 53% of the patients surveyed were non-adherers [69]. In both studies, several factors appeared to affect medication adherence. These included patients' genders, age and race as well as their medication knowledge, the total number of drugs prescribed, dosing frequencies and the level of co-morbidities. In a third study involving different healthcare professionals, non-adherence was top of the list of identified

Activity				HP Study	QoF						
Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
10 + 20mg	23.88	28.18	33.74	36.92	39.91	42.77	44.75	45.39	44.01	41.52	39.09
40 + 80mg	1.49	2.83	6.08	12.99	26.26	40.43	52.68	68.52	81.25	91.21	98.31

NB: HP = Heart Protection study and QoF=Quality and Outcomes Framework

Table 4: Dispensing of different tablet strengths of simvastatin (millions of tablets) among National Health Service patients in Scotland 2000 – 2010 (adapted from [27]).

medicine issues followed by incorrect administration of medicines [126]. This study also demonstrated the importance of pharmacists working in collaboration with other healthcare professionals, especially physicians, to identify and resolve pharmaceutical care issues to provide optimal care [126].

There have been a number of activities initiated by the Ministry of Health in Malaysia (MOH) to improve medication adherence in patients with diabetes. This includes producing information booklets as well as initiating medication adherence clinics [127]. These medication adherence clinics, or Medication Therapy Adherence Clinics (MTACs), are clinics manned by trained pharmacists located in the physician's clinic for 12 disease states including diabetes. The protocol for DMTAC (Diabetes MTACs) requires selected patients to attend the clinic at least once every three months for two years. These are typically problematic cases failing at routine care settings. As a result, they receive more intensive and personalised follow-up than seen during normal clinics. DMTAC patients have uncontrolled diabetes with HbA1c >8.0%, fasting blood glucose (FBS) > 6.1 mmol/l or 2 hours post prandial sugar level >8.0 mmol/l. They typically have co-morbidities including macrovascular and microvascular complications and are prescribed multiple medications. The objective of DMTAC clinics is to enhance the adherence to the medications prescribed as well as monitor any untoward side-effects. As previously discussed, good control of blood pressure and adequate dosing of statins can help reduce morbidity and mortality in these patients. Since its inception in 2004, up to 2013, there are 378 DMTACs with 10,532 patients attending such clinics either in hospitals or health clinics across Malaysia.

Cross-sectional studies have recently been performed to assess differences in subsequent adherence rates between patients attending DMTACs and a control group within government facilities. Facilities were categorized as National Referral Hospitals, State Hospitals, Hospitals with Specialists, Hospitals without Specialists and Health Clinics. A total of 2486 patients were included in the study through a systematic random selection process. The impact of DMTACs on education and adherence was assessed using the Morisky Medication Adherence Scale (MMAS-4) tool [128]. Odds-ratio analysis of non-adherence showed that race, household income and age were significant indicators for poor adherence. However, there appeared to be no significant difference in adherence rates between the two groups. There was also no corresponding significant increase in HbA1c control in the DMTAC versus control groups.

These findings may be in part due to differences in sample sizes and patient characteristics between the two groups, especially given the characteristics of patients referred to the DMTACs. They may also be due to the fact that patients were only seen once every three months, e.g. Rothman and colleagues in the US studied a total of 217 Type 2 DM patients with poor glycaemic control who received an intensive diabetes management from clinical pharmacists every 2 to 4 weeks for a period of 12 months. They did show a significant HbA1c reduction of 2.5% [129].

These findings and their implications are now being analysed since continuous medication counselling and monitoring the disease status of patients is seen as an essential component to reduce future morbidity and mortality in patients with diabetes. This could include agreed HbA1c goals for DMTAC patients as well as potentially greater intensity in the number and extent of patient visits, especially initially, with a number of studies showing a positive effect of such activities on glycaemic control [129-132].

This study also reviewed the impact of non-adherence on the accessibility and availability of medicines at the various health facilities. This is relevant since budgetary constraints can limit formulary listings and subsequently impact on medication use. The results showed that most of the essential anti-diabetic drugs (ADA) are listed at all health facilities and are being prescribed to patients. However, there were large differences in the cost of medications per patient between facilities, which was mainly due to differences in prescribed medications for patient co-morbidities. This study showed medication accessibility and availability for ADAs was not the main issue, which is important when looking to appropriately managing patients with diabetes and any associated co-morbid diseases to improve their outcomes.

Discussion

A number of inferences and conclusions can be drawn from the various case histories outlined in the four sub-sections. Firstly, regarding potential initiatives to enhance the prescribing of generics versus originators, the findings in Scotland provide an example of a long-term approach to enhance INN prescribing. As a result, reduce potential patient confusion if different branded generics are dispensed on different occasions. This is especially important if dispensers lack training on how to handle concerns with substitution and/ or do not receive adequate payment for providing relevant information to patients potentially limiting their time with them [45,86]. However, the example of HAAD shows that authorities must fully think through any measures else there could be disappointment with the outcomes [30].

The findings also suggest that both supply-side measures lowering the prices of generics to 2% to 10% of pre-patent loss prices, coupled with multiple demand-side reforms, can appreciably enhance prescribing efficiency for pertinent classes once generics become available in the class. They also demonstrate that the influence of demand-side measures appears to be additive as illustrated by greater prescribing efficiency for the PPIs in the Netherlands, Sweden and the UK (Scotland) with their multiple and intensive demand-side measures compared with the Republic of Ireland with fewer measures [27,36,46]. As mentioned, this resulted in expenditure in Ireland being over ten times that seen in Sweden when adjusted for population size for both the PPIs and statins, although the population in Ireland had greater co-morbidity [46]. A similar situation is seen with limiting the prescribing of ARBs versus generic ACEIs in Scotland compared with Portugal with its fewer demand-side measures [29]

No change initially in the utilisation of losartan post generics in NHS Bury, even though there had been initiatives generally among primary care groups in the UK to enhance the preferential prescribing of generics including generic ACEIs versus patented ARBs [29,44,45], was also seen in other European countries and regions. These included Ireland, Scotland and Spain (Catalonia). In each country there were also no specific activities encouraging the preferential prescribing of losartan [44,45,133]. This suggests that there is no spill over of learnings from one class to another to favourably affect physician prescribing habits. Consequently, multiple measures are needed to effect changes in prescribing habits. This mirrors the findings from other studies [44,134]. This finding may be mitigated to some extent on this occasion by the increased complexity in the message among health authorities, i.e. going from encouraging the prescribing of generic ACEIs first line versus patented ARBs to generic ACEIs and low cost ARBs first line versus patented ARBs [29,133,135].

The need to make considerable savings from the combination of

supply- and demand-side measures without compromising patient care is becoming increasingly important given the continual pressure on resources coupled with the desire of authorities to either increase patient access to medicines; alternatively, continue to provide equitable and comprehensive healthcare. All healthcare professionals play a key role with helping to achieve this. This includes pharmacists working with medicine management teams at local, regional or national health authorities. The active involvement of physicians is also important to achieve desired results. However, it is recognised there are classes where it is difficult to introduce demand-side measures due to the need to tailor pharmacotherapy to the individual patient, e.g. atypical antipsychotics [8].

The 'Wise List' approach within the Stockholm Metropolitan Healthcare Region shows that comprehensive strategies can be undertaken over time to improve the rational use of medicines (RUM). This includes improving the interface between hospital and ambulatory care. This has become increasingly important with many new premium priced drugs, including new biological drugs, initiated in hospital [51]. High adherence rates have been achieved through instigating programmes to access knowledge at the point of care, involving respected therapeutic experts and physicians in the development process, continuous medical education of prescribers around the 'Wise List' and the systematic approaches to the introduction of new medicines [50]. This pragmatic approach, linking prescribing guidance and advice for designated medicines – 'Wise Advice', also avoids guideline overload. Guideline overload was seen in France with their extensive number of guidelines for clinicians in ambulatory care, which eventually led to their demise [136,137]. As mentioned earlier, the same advice is given to health authorities when developing and instigating quality indicators [79]. The 'Wise List' has now been translated into Serbian to form part of the long term strategy of the Republic of Serbia's Health Insurance Fund to improve the quality of care in ambulatory care. Other countries could learn from such initiatives, especially those where there are currently few health authority initiatives to improve physician prescribing and subsequent patient care. The situation in the State of Minas Gerais with initiatives to improve the prescribing of medicines for patients with Alzheimer's Disease (Figure 2) will also be monitored to provide future guidance.

It is likely that we will also see increased activities pre- to post-launch for new medicines to optimise their use, especially where there are safety and/ or budgetary concerns. This builds on the situation with dabigatran [9,12].

The findings regarding the prescribed doses for statins make it essential for health authorities to monitor prescribed doses as more information becomes available. Otherwise, they may fail to achieve the desired result. The findings in South Africa suggest that potential under dosing may not be the same for all statins (Table 3), so targeted educational and other activities may be needed. The approach in the UK with multiple initiatives, including incentivising physicians to achieve lipid target levels, may be one way forward if pertinent (Table 4).

The findings initially in Lithuania as well as in Pakistan suggest it is also essential for health authorities to introduce policies to enhance patient access to low cost generic statins and other pertinent medications to reduce the morbidity and mortality associated with chronic NCDs. Otherwise, they may fail to reach their desired objectives. The findings in Lithuania regarding the appreciable difference in the utilisation of statins and renin-angiotensin inhibitor medicines (Table 5), as well as the considerable difference in statin utilisation between Lithuania and the UK, make it mandatory for authors to report associated policies when undertaking cross national utilisation studies else there could be concerns with the validity of the data [121].

Country	DIDs in 2007
Austria	113.3
Croatia	104.3
Lithuania	111.3
Portugal	191.8
Scotland	165.5
Spain (Catalonia)	152.9
Sweden	116.8

Table 5: Comparison of the utilisation of renin-angiotensin inhibitor drugs among European countries in 2007 (DIDs) [29,121].

Once these policies are in place, strategies should be aimed at enhancing adherence especially in patients with chronic asymptomatic diseases. The activities by the Ministry of Health in Malaysia to improve medication adherence in patients with chronic diseases [MTACs] including diabetes [DMTACs] also provides direction to other countries seeking to reduce morbidity and mortality associated with NCDs. However, the situation is complex with typically multiple strategies needed [63,64,124]. In addition, patient values should also be explored including their priorities, life philosophy and their background to improve future adherence rates [138]. The studies described also show it is imperative for the authorities to monitor the impact of their interventions in order to review and plan pertinent further activities if the desired results are not being achieved. Otherwise, they may fail to reach their desired outcomes.

In conclusion, a number of case histories demonstrating potential ways for all key stakeholder groups to enhance prescribing efficiency have been discussed to provide future guidance. These also include learnings from case histories where the desired results have not been achieved, and potential ways forward. We believe it is increasingly important for countries and regions to learn from each other in the face of growing resource pressures. Without such learnings, countries may well struggle to continue to increase patient access or continue to provide comprehensive and equitable healthcare.

Acknowledgements and Financial Disclosure

There are no conflicts of interest from any author. However, the majority of authors are employed by health authorities, health insurance companies, universities or Physician Associations or are advisers to them.

This work was in part supported by grants from the Karolinska Institutet, Sweden.

References

1. Babar ZU, Francis S (2014) Identifying priority medicines policy issues for New Zealand: a general inductive study. BMJ Open 4: e004415.
2. Drews J (2000) Drug discovery: a historical perspective. Science 287: 1960-1964.
3. Mousnad MA, Shafie AA, Ibrahim MI (2014) Systematic review of factors affecting pharmaceutical expenditures. Health policy (Amsterdam, Netherlands) 116: 137-146.
4. Godman B, Campbell S, Suh HS, Finlayson A, Bennie M, Gustafsson L (2013) Ongoing measures to enhance prescribing efficiency across Europe: implications for other countries. J Health Tech Assess 1: 27-42.
5. OECD (2011) OECD, Health at a Glance: OECD Indicators. Pharmaceutical expenditure OECD Publishing.
6. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R (2009) Medicine prices,

availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet 373: 240-249.

7. Garattini S, Bertele' V, Godman B, Haycox A, Wettermark B, et al. (2008) Enhancing the rational use of new medicines across European health care systems. Eur J Clin Pharmacol 64: 1137-1138.
8. Godman B, Petzold M, Bennett K, Bennie M, Bucsics A, Finlayson AE, et al. (2014) Can authorities appreciably enhance the prescribing of oral generic risperidone to conserve resources? Findings from across Europe and their implications. BMC medicine 12: 98.
9. Godman B, Malmström RE, Diogene E, Jayathissa S, McTaggart S, et al. (2014) Dabigatran - a continuing exemplar case history demonstrating the need for comprehensive models to optimize the utilization of new drugs. Front Pharmacol 5: 109.
10. Garuoliene K, Godman B, Gulbinovic J, Wettermark B, Haycox A (2011) European countries with small populations can obtain low prices for drugs: Lithuania as a case history. Expert Rev Pharmacoecon Outcomes Res 11: 343-349.
11. Garuoliene K, Alonderis T, Marcinkevicius M (2011) Pharmaceutical policy and the effects of the economic crisis: Lithuania. EuroHealth 17: 1-4.
12. Malmström RE, Godman BB, Diogene E, Baumgärtel C, Bennie M, et al. (2013) Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs. Front Pharmacol 4: 39.
13. Evaluate Pharma (2012) Surveying Tomorrow's BioPharma Landscape. The NASDAQ Biotech Index Up Close.
14. Experts in Chronic Myeloid Leukemia (2013) The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood 121: 4439-4442.
15. Cohen P, Felix A (2014) Are payers treating orphan drugs differently? Journal of Market Access & Health Policy 2: 23513
16. Cohen D, Raftery J (2014) Paying twice: questions over high cost of cystic fibrosis drug developed with charitable funding. BMJ 348: g1445.
17. Godman B, Paterson K, Malmstrom RE, Selke G, Fagot JP, et al. (2012) Improving the managed entry of new medicines: sharing experiences across Europe. Expert review of pharmacoeconomics & outcomes research 12: 439-41.
18. Ferrario AKP (2013) Managed entry agreements for pharmaceuticals: The European experience: LSE.
19. Klemp M, Frønsdal KB, Facey K; HTAi Policy Forum (2011) What principles should govern the use of managed entry agreements? Int J Technol Assess Health Care 27: 77-83.
20. Guerra AA Jr, Cesar CC, Cherchiglia ML, Andrade EI, de Queiroz OV, et al. (2010) Cyclosporine versus tacrolimus in immunosuppressive maintenance regimens in renal transplants in Brazil: survival analysis from 2000 to 2004. Ann Pharmacother 44: 192-201.
21. Raaschou P, Simard JF, Holmqvist M, Askling J (2013) Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. BMJ 346: f1939.
22. Nijsten T, Wakkee M (2008) Psocare: Italy shows the way in postmarketing studies. Dermatology 217: 362-364.
23. Wettermark B, Brandt L, Kieler H, Boden R (2014) Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment. International journal of clinical practice 68: 104-110.
24. Qvarnström M, Kahan T, Kieler H, Brandt L, Hasselström J, et al. (2013) Persistence to antihypertensive drug treatment in Swedish primary healthcare. Eur J Clin Pharmacol 69: 1955-1964.
25. Forslund T, Raaschou P, Hjemdahl P, Krakau I, Wettermark B (2011) Usage, risk, and benefit of weight-loss drugs in primary care. J Obes 2011: 459263.
26. Adamski J, Godman B, Ofierska-Sujkowska G, Osinska B, Herholz H, et al. (2010) Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC health services research 10: 153.
27. Bennie M, Godman B, Bishop I, Campbell S (2012) Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. Expert review of pharmacoeconomics & outcomes research 12: 125-130.
28. McGinn D, Godman B, Lonsdale J, Way R, Wettermark B, et al. (2010) Initiatives to enhance the quality and efficiency of statin and PPI prescribing in the UK: impact and implications. Expert Rev Pharmacoecon Outcomes Res 10: 73-85.
29. Voncina L, Strizrep T, Godman B, Bennie M, Bishop I, et al. (2011) Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future. Expert review of pharmacoeconomics & outcomes research 11: 469-479.
30. Abuelkhair M, Abdu S, Godman B, Fahmy S, Malmstrom RE, et al. (2012) Imperative to consider multiple initiatives to maximize prescribing efficiency from generic availability: case history from Abu Dhabi. Expert review of pharmacoeconomics & outcomes research 12: 115-124.
31. Andersson K, Sonesson C, Petzold M, Carlsten A, Lönnroth K (2005) What are the obstacles to generic substitution? An assessment of the behaviour of prescribers, patients and pharmacies during the first year of generic substitution in Sweden. Pharmacoepidemiol Drug Saf 14: 341-348.
32. Godman B, Wettermark B, Hoffmann M, Andersson K, Haycox A, et al. (2009) Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance. Expert review of pharmacoeconomics & outcomes research 9: 65-83.
33. Wettermark B, Godman B, Andersson K, Gustafsson LL, Haycox A, et al. (2008) Recent national and regional drug reforms in Sweden: implications for pharmaceutical companies in Europe. Pharmacoeconomics 26: 537-550.
34. Godman B, Abuelkhair M, Vitry A, Abdu S, Bennie M, Bishop I, et al. (2012) Payers endorse generics to enhance prescribing efficiency; impact and future implications, a case history approach. GaBI 1: 21-35.
35. Fraeyman J, Van Hal G, Godman B, Beutels P (2013) The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium. Expert review of pharmacoeconomics & outcomes research 13: 141-51.
36. Woerkom M, Piepenbrink H, Godman B, Metz J, Campbell S, et al. (2012) Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. Journal of comparative effectiveness research 1: 527-538.
37. Godman B, Schwabe U, Selke G, Wettermark B (2009) Update of recent reforms in Germany to enhance the quality and efficiency of prescribing of proton pump inhibitors and lipid-lowering drugs. Pharmacoeconomics 27: 435-438.
38. Sakshaug S, Furu K, Karlstad Ø, Rønning M, Skurtveit S (2007) Switching statins in Norway after new reimbursement policy: a nationwide prescription study. Br J Clin Pharmacol 64: 476-481.
39. Kiviniemi V, Peura P, Helin-Salmivaara A, Martikainen JE, Hartikainen J, et al. (2011) Suboptimal use of statins at treatment initiation. Eur J Clin Pharmacol 67: 971-973.
40. Usher-Smith J, Ramsbottom T, Pearmain H, Kirby M (2008) Evaluation of the clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a primary care setting: 2 years on. International journal of clinical practice 62: 480-484.
41. Moon JC, Flett AS, Godman BB, Grosso AM, Wierzbicki AS (2010) Getting better value from the NHS drug budget. BMJ 341: c6449.
42. Martikainen JE, Saastamoinen LK, Korhonen MJ, Enlund H, Helin-Salmivaara A (2010) Impact of restricted reimbursement on the use of statins in Finland: a register-based study. Med Care 48: 761-766.
43. Weng TC, Yang YH, Lin SJ, Tai SH (2010) A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 35: 139-151.
44. Godman B, Bishop I, Finlayson AE, Campbell S, Kwon HY, et al. (2013) Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries. Expert review of pharmacoeconomics & outcomes research 13: 469-482.
45. Martin A, Godman B, Miranda J, Tilstone J, Saleem N, Olsson E, et al. (2014) Measures to improve angiotensin receptor blocker prescribing efficiency in the

UK: findings and implications. Journal of comparative effectiveness research 3: 41-51.

46. Godman B, Shrank W, Andersen M, Berg C, Bishop I, et al. (2010) Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. Expert review of pharmacoeconomics & outcomes research 10: 707-722.

47. Frank RG (2007) The ongoing regulation of generic drugs. N Engl J Med 357: 1993-1996.

48. Jack A (2008) Balancing Big Pharma's books. BMJ 336: 418-419.

49. Godman B, Bennie M, Baumgärtel C, Sovic Brkicic L, et al. (2012) Essential to increase the use of generics in Europe to maintain comprehensive healthcare? Farmeconomia: Health Economics and Therapeutic Pathways 13 (Suppl 3): 5-20.

50. Gustafsson LL, Wettermark B, Godman B, Andersen-Karlsson E, Bergman U, et al. (2011) The 'wise list'- a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. Basic & clinical pharmacology & toxicology 108: 224-33.

51. Bjorkhem-Bergman L, Andersen-Karlsson E, Laing R, Diogene E, Melien O, et al. (2013) Interface management of pharmacotherapy. Joint hospital and primary care drug recommendations. European journal of clinical pharmacology. 69 Suppl 1: 73-78.

52. Rottenkolber D, Schmiedl S, Rottenkolber M, Farker K, Salje K, et al. (2011) Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. Pharmacoepidemiology and drug safety 20: 626-634.s

53. Pirmohamed M, James S, Meakin S, Green C, Scott AK, et al. (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329: 15-19.

54. Miller I Ashton-Class J, Fert V, et al. (2011) Market access challenges in the EU for high medical value diagnostic tests. Personalised Medicine 8: 137-148.

55. Wensing M, Broge B, Riens B, Kaufmann-Kolle P, Akkermans R, et al. (2009) Quality circles to improve prescribing of primary care physicians. Three comparative studies. Pharmacoepidemiology and drug safety 18: 763-769.

56. Niquille A, Ruggli M, Buchmann M, Jordan D, Bugnon O (2010) The nine-year sustained cost-containment impact of swiss pilot physicians-pharmacists quality circles. Ann Pharmacother 44: 650-657.

57. Chhina HK, Bhole VM, Goldsmith C, Hall W, Kaczorowski J, et al. (2013) Effectiveness of academic detailing to optimize medication prescribing behaviour of family physicians. Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques 16: 511-529.

58. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, et al. (2007) Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database Syst Rev : CD000409.

59. Godman B, Finlayson AE, Cheema PK, Zebedin-Brandl E, Gutiérrez-Ibarluzea I, et al. (2013) Personalizing health care: feasibility and future implications. BMC Med 11: 179.

60. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, et al. (2010) Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 376: 975-983.

61. UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317: 703-713.

62. Perreault S, Dragomir A, Blais L, Berard A, Lalonde L, White M, et al. (2009) Impact of better adherence to statin agents in the primary prevention of coronary artery disease. European journal of clinical pharmacology 65: 1013-1024.

63. Brown MT, Bussell JK (2011) Medication adherence: WHO cares? Mayo Clin Proc 86: 304-314.

64. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X (2008) Interventions for enhancing medication adherence. Cochrane Database Syst Rev : CD000011.

65. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM (2008) The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. Int J Clin Pract 62: 76-87.

66. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, et al. (2008) Medication compliance and persistence: terminology and definitions. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 11: 44-47.

67. Kontopantelis E, Reeves D, Valderas JM, Campbell S, Doran T (2013) Recorded quality of primary care for patients with diabetes in England before and after the introduction of a financial incentive scheme: a longitudinal observational study. BMJ quality & safety 22: 53-64.

68. Doran T, Fullwood C, Gravelle H, Reeves D, Kontopantelis E, et al. (2006) Pay-for-performance programs in family practices in the United Kingdom. N Engl J Med 355: 375-384.

69. Ahmad NS, Ramli A, Islahudin F, Paraidathathu T (2013) Medication adherence in patients with type 2 diabetes mellitus treated at primary health clinics in Malaysia. Patient Prefer Adherence 7: 525-530.

70. European Directorate for the Quality of Medicines & HealthCare E. Pharmaceutical Care - Policies and Practices for a Safer, More Responsible and Cost-effective Health System.

71. Moe-Byrne T, Chambers D, Harden M, McDaid C (2014) Behaviour change interventions to promote prescribing of generic drugs: a rapid evidence synthesis and systematic review. BMJ Open 4: e004623.

72. Brennan N, Mattick K (2013) A systematic review of educational interventions to change behaviour of prescribers in hospital settings, with a particular emphasis on new prescribers. British journal of clinical pharmacology 75: 359-372.

73. Dylst P, Vulto A, Godman B, Simoens S (2013) Generic medicines: solutions for a sustainable drug market? Appl Health Econ Health Policy 11: 437-443.

74. Dylst P, Vulto A, Simoens S (2014) Analysis of European policy towards generic medicines. Generics and Biosimilars Initiative Journal. 3: 34-35.

75. Vogler S (2012) The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries-an overview. Generics and biosimilars Initiative Journal (GaBI Journal) 1: 93-100.

76. Dylst P, Simoens S (2011) Does the market share of generic medicines influence the price level?: a European analysis. Pharmacoeconomics 29: 875-882.

77. Godman B, Shrank W, Andersen M, Berg C, Bishop I, et al. (2011) Policies to enhance prescribing efficiency in europe: findings and future implications. Front Pharmacol 1: 141.

78. Abernethy D, Birkett D, Brosen K, Cascorbi I, Gustafsson LL, Hoppu K, et al.. Clinical pharmacology in health care, teaching and research.

79. Campbell SM, Godman B, Diogene E, Fürst J, Gustafsson LL, et al. (2014) Quality Indicators as a Tool in Improving the Introduction of New Medicines. Basic Clin Pharmacol Toxicol Doi: 10.1111/bcpt.12295.

80. Godman B, Wettermark B, van Woerkom M, Fraeyman J, Alvarez-Madrazo S, et al. (2014) Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. Frontiers in pharmacology 5: 106.

81. Baumgartel C, Godman B, Malmström R, Andersen M, et al. (2012) What lessons can be learned from the launch of generic clopidogrel? GaBI Journal 1: 58-68.

82. Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, et al. (2008) Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA 300: 2514-2526.

83. Kesselheim AS, Stedman MR, Bubrick EJ, Gagne JJ, Misono AS, et al. (2010) Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis. Drugs 70: 605-621.

84. Ferner RE, Lenney W, Marriott JF (2010) Controversy over generic substitution. BMJ 340: c2548.

85. Duerden MG, Hughes DA (2010) Generic and therapeutic substitutions in the UK: are they a good thing? Br J Clin Pharmacol 70: 335-341.

86. Olsson E, Kälvemark Sporrong S (2012) Pharmacists' experiences and attitudes regarding generic drugs and generic substitution: two sides of the coin. Int J Pharm Pract 20: 377-383.

87. Olsson E, Ingman P, Ahmed B, Kälvemark Sporrong S (2014) Pharmacist-patient communication in Swedish community pharmacies. Res Social Adm Pharm 10: 149-155.

88. Vandoros S (2014) Therapeutic substitution post-patent expiry: the cases of ace inhibitors and proton pump inhibitors. Health Econ 23: 621-630.

89. Godman B, Sakshaug S, Berg C, Wettermark B, Haycox A (2011) Combination of prescribing restrictions and policies to engineer low prices to reduce reimbursement costs. Expert Rev Pharmacoecon Outcomes Res 11: 121-129.

90. Heran BS, Wong MM, Heran IK, Wright JM (2008) Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev : CD003822.

91. MeReC (2011) NICE updates its guidance on the management of hypertension.

92. Godman B, Wettermark B, Miranda J, Bennie M, Martin A, et al. (2013) Influence of multiple initiatives in Sweden to enhance ARB prescribing efficiency following generic losartan; findings and implications for other countries. International journal of clinical practice 67: 853-862.

93. Svanström H, Pasternak B, Hviid A (2012) Association of treatment with losartan vs candesartan and mortality among patients with heart failure. JAMA 307: 1506-1512.

94. Wettermark B, Godman B, Jacobsson B, Haaijer-Ruskamp FM (2009) Soft regulations in pharmaceutical policy making: an overview of current approaches and their consequences. Applied health economics and health policy 7:137-147.

95. Wettermark B, Godman B, Neovius M, Hedberg N, Mellgren TO, et al. (2010) Initial effects of a reimbursement restriction to improve the cost-effectiveness of antihypertensive treatment. Health Policy 94: 221-229.

96. Wettermark B, Pehrsson A, Juhasz-Haverinen M, Veg A, Edlert M, et al. (2009) Financial incentives linked to self-assessment of prescribing patterns: a new approach for quality improvement of drug prescribing in primary care. Qual Prim Care 17: 179-189.

97. Godman B, Bucsics A, Burkhardt T, Piessnegger J, Schmitzer M, et al. (2013) Potential to enhance the prescribing of generic drugs in patients with mental health problems in austria; implications for the future. Front Pharmacol 3: 198.

98. Norman C, Zarrinkoub R, Hasselström J, Godman B, Granath F, et al. (2009) Potential savings without compromising the quality of care. Int J Clin Pract 63: 1320-1326.

99. Böttiger Y, Laine K, Andersson ML, Korhonen T, Molin B, et al. (2009) SFINX-a drug-drug interaction database designed for clinical decision support systems. Eur J Clin Pharmacol 65: 627-633.

100. Eiermann B, Rahmner P, Korkmaz S. Knowledge Bases for Clinical Decision Support in Drug Prescribing – Development, Quality Assurance, Management, Integration, Implementation and Evaluation of Clinical Value. Computer and Information Science, Numerical Analysis and Scientific Computing - "Decision Support Systems".

101. Loganathan M, Singh S, Franklin BD, Bottle A, Majeed A (2011) Interventions to optimise prescribing in care homes: systematic review. Age Ageing 40: 150-162.

102. Van Hoof TJ, Miller NE, Meehan TP (2013) Do published studies of educational outreach provide documentation of potentially important characteristics? American journal of medical quality : the official journal of the American College of Medical Quality 28: 480-484.

103. Faria C, Wenzel M, Lee KW, Coderre K, Nichols J, et al. (2009) A narrative review of clinical inertia: focus on hypertension. J Am Soc Hypertens 3: 267-276.

104. Bajcetic M, Kalaba M, Godman B, Sipetic T, et al. Ongoing programmes to reduce the high rate of antibiotic consumption in Serbia; current situation and future direction. Pharmacoepidemiology and drug safety 21 (Suppl 3): 98.

105. Wladysiuk M, Araszkiewicz A, Godman B, Szabert K, Barbui C, et al. (2011) Influence of patient co-payments on atypical antipsychotic choice in Poland: implications once generic atypicals are available. Applied health economics and health policy 9: 101-110.

106. Ezenduka C, Ubochi V, Ogbonna B (2014) The Utilization Pattern and Costs Analysis of Psychotropic Drugs at a Neuropsychiatric Hospital in Nigeria. British Journal of Pharmaceutical Research 4: 325-337.

107. Godman B, Ezenduka C, Bennie M, Persson M, Wladysiuk M, Barbui C (2014) BARRIERS TO THE OPTIMAL USE OF PHARMACOTHERAPY TO MANAGE DEPRESSION AND SCHIZOPHRENIA: IMPLICATIONS AND FUTURE DIRECTION. Basic & clinical pharmacology & toxicology 115 (Suppl 1): 180.

108. Ozieranski P, McKee M, King L (2012) Pharmaceutical lobbying under postcommunism: universal or country-specific methods of securing state drug reimbursement in Poland? Health Econ Policy Law 7: 175-195.

109. Davis C, Abraham J (2013) Is there a cure for corporate crime in the drug industry? BMJ 346: f755.

110. Yu SY, Yang BM, Kim JH (2013) New anti-rebate legislation in South Korea. Applied health economics and health policy 11: 311-318.

111. Brkicic LS, Godman B, Voncina L, Sovic S, Relja M (2012) Initiatives to improve prescribing efficiency for drugs to treat Parkinson's disease in Croatia: influence and future directions. Expert review of pharmacoeconomics & outcomes research 12: 373-384.

112. Legrand M1, Mateo J, Aribaud A, Ginisty S, Eftekhari P, et al. (2011) The use of dabigatran in elderly patients. Arch Intern Med 171: 1285-1286.

113. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, et al. (2014) The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). Journal of the American College of Cardiology 63: 321-328.

114. Joppi R, Cinconze E, Mezzalira L, Pase D, Poggiani C, et al. (2013) Hospitalized patients with atrial fibrillation compared to those included in recent trials on novel oral anticoagulants: a population-based study. European journal of internal medicine 24: 318-323.

115. Feely J, Bennett K (2008) Epidemiology and economics of statin use. Ir Med J 101: 188-191.

116. Mantel-Teeuwisse AK, Klungel OH, Schalekamp T, Verschuren WM, Porsius AJ, et al. (2005) Suboptimal choices and dosing of statins at start of therapy. Br J Clin Pharmacol 60: 83-89.

117. Hartz I, Sakshaug S, Furu K, Engeland A, Eggen AE, et al. (2007) Aspects of statin prescribing in Norwegian counties with high, average and low statin consumption - an individual-level prescription database study. BMC clinical pharmacology 7: 14.

118. Truter I (2014) Prescribed Daily Doses (PDDs) of Hypolipidaemic Agents in South Africa with Emphasis on HMG CoA Reductase Inhibitors. Journal of Health Science 4: 11-17.

119. SIGN. Management of diabetes - quick reference guide (2010).

120. SIGN. Heart Disease (2012 - updated from 2007.

121. Godman B, Garuoliene K, Gulbinovic J, Wettermark B (2011) Care needed when undertaking drug utilisation studies using commercial and administrative databases? Pharmacoepidemiology and drug safety 20: S167-168

122. Godman B, Hussain S, Mahmood S, Malik F (2014) Current challenges to the management of CV diseases in Pakistan; implications for the future. Basic & clinical pharmacology & toxicology 115: 16.

123. Kaplan W, Wirtz V, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R (2013) Priority Medicines for Europe and the World 2013.

124. Mitchell A, Selmes T (2007) Why don't patients take their medicine? Reasons and solutions in psychiatry. Advances in Psychiatric Treatment. 13: 336-46.

125. Ramli A, Ahmad NS, Paraidathathu T (2012) Medication adherence among hypertensive patients of primary health clinics in Malaysia. Patient Prefer Adherence 6: 613-622.

126. Chua SS, Kok LC, Yusof FA, Tang GH, Lee SW, et al. (2012) Pharmaceutical care issues identified by pharmacists in patients with diabetes, hypertension or hyperlipidaemia in primary care settings. BMC Health Serv Res 12: 388.

127. Ministry of Health, Malaysia (2010) Protocol - Medication therapy adherence clinic: diabetes.

128. Morisky DE, Green LW, Levine DM (1986) Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 24: 67-74.

129. Rothman RL, Malone R, Bryant B, Shintani AK, Crigler B, et al. (2005) A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. The American journal of medicine 118: 276-84.

130. Dorland K, Liddy C (2014) A pragmatic comparison of two diabetes education programs in improving type 2 diabetes mellitus outcomes. BMC Res Notes 7: 186.

131. Thongsai S, Youjaiyen M (2013) The long-term impact of education on diabetes for older people: a systematic review. Glob J Health Sci 5: 30-39.

132. Worswick J, Wayne SC, Bennett R, Fiander M, Mayhew A, et al. (2013) Improving quality of care for persons with diabetes: an overview of systematic reviews - what does the evidence tell us? Syst Rev 2: 26.

133. Bennie M, Bishop I, Godman B, Campbell S, Miranda J, et al. (2013) Are prescribing initiatives readily transferable across classes: the case of generic losartan in Scotland? Qual Prim Care 21: 7-15.

134. Godman B, Wettermark B, van Woerkom M, Fraeyman J, Alvarez-Madrazo S, Berg C, et al. (2014) Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. Frontiers in Pharmacology Focused Review 5 (Article 106): 1-9.

135. Moon J, Godman B, Petzold M, Alvarez-Madrazo S, Bennett K, Bishop I et al (2014) Different initiatives across Europe to enhance losartan utilisation post generics: impact and implications. *Frontiers in pharmacology* **5**: 1-10.

136. Allen D, Harkins KJ (2005) Too much guidance? Lancet 365: 1768.

137. Sermet C, Andrieu V, Godman B, Van Ganse E, Haycox A, et al. (2010) Ongoing pharmaceutical reforms in France: implications for key stakeholder groups. Applied health economics and health policy 8: 7-24.

138. Lee YK, Low WY, Ng CJ (2013) Exploring patient values in medical decision making: a qualitative study. PLoS One 8: e80051.

Citation: Godman B, Acurcio FA, Guerra Júnior AA, Alvarez-Madrazo S, Faridah Aryani MY, et al. (2014) Initiatives among Authorities to Improve the Quality and Efficiency of Prescribing and the Implications. J Pharma Care Health Sys 1: 113. doi:10.4172/jpchs.1000113