amrc

ASSOCIATION OF MEDICAL RESEARCH CHARITIES

Facilitating adoption of off-patent, repurposed medicines into NHS clinical practice

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FOREWORD

A foreword from Aisling Burnand MBE, Chief Executive of AMRC

Medical research is increasingly focusing on how existing medicines, licensed for use in treating particular conditions, can also be investigated for use in treating other conditions. Two examples in the report, bisphosphonates for preventing secondary breast cancer and docetaxel (in addition to standard hormone therapy) in metastatic prostate cancer, demonstrate the cost-effective and life-extending benefits to patients.

In the case of bisphosphonates, a study showed that giving a bisphosphonate to post-menopausal women with primary breast cancer could reduce the risk of breast cancer spreading to the bone within 10 years by nearly a third; reduce the risk of breast cancer spreading to any site, including the bone, within 10 years by around a fifth; and reduce the risk of death from breast cancer within 10 years by a sixth.

Research is promising and indicates that there could be many other disease areas and patients that could benefit from the use of off-patent medicines. Promising areas include those affected by multiple sclerosis and Parkinson's disease.

Facilitating access to off-patent medicines

Prescribers, patients and NHS services may want to use off-patent medicines that have been identified through new research and evidence to have potential therapeutic use for patients. However, without access to information and support prescribers may not pursue these treatment options for patients. The report provides information about the existing frameworks which support this within current legal and safety systems.

This report provides insights about the repurposing of off-patent medicines, including how the drug regulation system and national bodies can support it and how to navigate the different routes that support access to repurposed drugs for NHS patients. It is currently the case that outside the licensed use of a medicine, existing frameworks for off-patent use are available to prescribers and their patients. Yet, greater support is needed to help prescribers and the respective commissioning bodies in their decision-making on the use of off-patent medicines, where this is clinically appropriate. This report, therefore, aims to highlight the support that is already available to prescribers and commissioners, and outlines a framework to improve access to repurposed medicines for patients.

Taking forward recommendations in the report

The recommendations in the report are those of the Drug Repurposing Group (see Annex A for membership) and reflect the range of stakeholders involved in off-patent medicines use and drug regulation, including for the MHRA, Regional Medicines Optimisation Committees and the British National Formulary.

It also proposes potential financial incentives for generic medicines manufacturers to participate in medicines repurposing. For instance, extending the scope of HMRC Research & Development Tax Credits to include repurposing of generic medicines and exploring a UK Catalyst Fund to establish the UK as a leader in medicines repurposing. This would address a key challenge in improving access to off-patent medicines for patients, once a medicine's patent has expired. Such incentives could support the costs involved in licencing a repurposed off-patent medicine.

I was pleased to note that repurposed medicines are included in the potential technologies to be considered for the Accelerated Access Pathway (AAP), as set out in the Government's response to the Accelerated Access Review.

The Group's report is the first step on the path to ensuring that patients can benefit from off-patent, repurposed medicines. Going forward, I recommend that all stakeholders continue to work together to create an environment that results in the rapid uptake of repurposed medicines when new evidence shows a clear benefit to patients.

1. EXECUTIVE SUMMARY

1.1 **Greater advice and support is needed for organisations and individuals who may want to use a licensed, off-patent, medicine[1] in an indication outside its licence where research has shown value for treatment of identified conditions.** Some well-established off-patent medicines are identified through new research and evidence to have potential therapeutic use outside their licensed indications, a process which we describe here as "drug repurposing". Prescribers and patients, and the NHS services that support them, may want to make use of these medicines in these new indications. However, they do not always have the information and support to pursue this. Generally, such a new indication will need to be established through a new or updated regulatory licence for that indication. The incentives for manufacturers to develop and pursue a licence for these new indications can be limited. Other organisations, such as medical research charities, may also want to pursue licences, but need guidance through the process. Outside licensed use, existing frameworks for off-label use are available to prescribers and their patients, but greater support is needed to help them and their commissioning bodies in their decision-making.

1.2 **This report provides some insights about repurposing of off-patent medicines, including how the drug regulation system and national bodies can support it. It also provides advice about how to navigate the different routes that support access to repurposed drugs for NHS patients**. Patients are prescribed off-label medicines on an individual, case-by-case basis, and under the discretion (and liability) of the prescriber and pharmacist supporting that patient. Prescribers need to be aware of the evidence supporting off-label use and feel confident in discussing the benefits and risks with the patient, and obtaining their consent to prescribe. All healthcare professionals should be aware of their indemnity and liability cover. The British National Formulary (BNF) notes that prescribing medicines outside the recommendations of their licence alters the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines as well as informing the patient or their carer that the prescribed medicine is off-label.

1.3 **As far as possible, medicines should be prescribed within the terms of the Marketing Authorisation (MA – also known as a "licence"). In line with EU law[2], the primary route to repurposing for establishing a new indication for a medicine is through the medicines licensing system**. The licensing system ensures that patients receive medicines that have been scientifically assessed to meet published European standards of safety,

[1] References to a product being "off-patent" include - in addition to the product no longer benefitting from any patent protection - references to it no longer benefitting from any periods of exclusivity provided for in medicines legislation, such as data or marketing exclusivity.

[2] The supply of medicines for unauthorised uses is an exception to the requirement that a medicine should either possess a marketing authorisation or be used in the context of clinical trials. Unlicensed uses of a medicine may, at the option of Member States, be allowed in order to fulfil a special need, in response to a bona fide solicited order from an authorised healthcare professional in order to treat their individual patient's special needs (Article 5.1 of Directive 2001/83/EC). Available at: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF

efficacy and quality. These standards are applied and enforced in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA). Medicines licensed by MHRA include approved information to assist patients and health professionals. Licensed medicines are also subject to pharmacovigilance (post-licensing monitoring of side effects) and can have specific risk management plans to ensure they are safely used.

1.4 **MHRA can provide practical advice on the levels of evidence required to license new uses**. Seeking and following MHRA advice at an early stage of development helps ensure clinical research programmes are designed in a way that supports achieving licensing. In some cases, joint scientific advice from MHRA and the National Institute for Health and Care Excellence (NICE) may be appropriate to help facilitate clinical research programmes which generate the evidence for licensing and the demonstration of clinical and cost effectiveness compared to other available treatments.

1.5 **In some specific circumstances[3], a medicine can be used off-label under current provisions that allow for prescribers to treat their patient, if supported by evidence, patient engagement and appropriate risk management.** There is evidence that prescribers, patients and commissioning bodies would benefit from greater support in decision-making, therefore aiding NHS teams to use off-label medicines. **This report seeks to provide greater clarity to guide appropriate off-label medicine use.** It includes a framework of information and support through which patient access to off-label repurposed drugs can be improved**.** Medical research charities and NICE have led the design and development of this framework, which for ease of reference is from here referred to as the **'drug repurposing framework'**. This route is built on existing national processes and is more systematic than arrangements that are made ad-hoc and may result in varied levels of patient access.

1.6 **Drugs used off-label through the systematic drug repurposing framework must meet key criteria.** They must be off-patent, the formulation licensed in the UK for at least one indication already, be intended for repurposing, have a body of robust published evidence available to support their use in the new indication and no licensed medicine is available for the indication being considered.

1.7 **This report outlines the elements of the drug repurposing framework to facilitate patient access through improved information and support.** These include alerting NICE to the treatment evidence, deciding on an assessment process (with transparent decision-making criteria), referral of the indication to the NHS for commissioning advice, ensuring healthcare professionals have relevant information on the risks and benefits of the treatment and ultimately providing appropriate access for the patient.

1.8 **The work on clarifying the routes to improve access to repurposed medicines began by mapping existing mechanisms and processes.** The

[3] EU Directive 2001/83/EC available at: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF

majority of this was done by NICE in relation to their medicines networks, systems and tools, the BNF in relation to a new approach to presenting off-label medicines in a standard way and the General Medical Council (GMC) in relation to their production of a 'Hot Topic' forum on the issue of off-label prescribing in November 2015.

1.9 **This report provides the recommendations of the Drug Repurposing Group which are all aimed at helping to ensure that the benefits of medical research are translated into practice to help improve outcomes for patients**. The recommendations present the different ways in which organisations and individuals can work with the MHRA to pursue a licensing route. Other recommendations include developing financial incentives that encourage generic manufacturers to participate in drug repurposing and pilot schemes to test the suitability and sustainability of the repurposing framework that enables appropriate off-label use of medicines.

1.10 Public bodies participated in meetings of the Drug Repurposing Group and have ensured factual accuracy of information in the report relating to the operation of schemes and processes that they own. The Department of Health provided secretariat for the group which was chaired by Aisling Burnand, of the Association of Medical Research Charities (AMRC). The report is an independent report presented to Ministers by Aisling Burnand in November 2017.

2. INTRODUCTION

2.1 Currently in England, routine access for patients receiving treatment on the NHS to new medicines is achieved by licensing the medicine. This is accompanied by a positive recommendation from NICE through its technology appraisal or guidelines process.

2.2 Where medicines are licensed, and have been shown to be clinically effective in a new indication which is not covered by the licence, then access is on an individual, case-by-case basis. This depends on the clinical needs of the individual patient, as assessed by the prescriber. This is referred to as off-label use. Although MHRA does not recommend off-label use, it has published recommendations on a 'prescribing hierarchy' for licensed, off-label and unlicensed medicines.

> **Off-label** – a licensed medicinal product or drug which is being used outside its licensed indications, e.g. for a patient who is not among the patient group named on the licence or to treat a medical condition which is not included in the licence or in a dosage which is different from that specified on the licence.

2.3 Off-label use relies on the clinician being aware of information on the risks and benefits of the 'off-label' use of the medicine and following the GMC's advice on such use, including the need for informed consent from the patient. This has resulted in highly variable patient access, and can cause significant duplication of effort for prescribers and administrators (particularly where the condition is common). Often new evidence takes a long time to reach all parts of the NHS. We have investigated the factors at play in repurposing to produce this report to help facilitate routine access for patients to off-patent, repurposed medicines in the NHS using existing mechanisms.

2.4 The purpose of this report is to:

- Provide some insights into drug repurposing;
- Improve outcomes for patients and to improve patient access;
- Describe how the drug regulation system and national bodies can support repurposing;
- Detail the work of, and share the outputs, from the Drug Repurposing Group; and
- Make recommendations about next steps.

2.5 Medical research is increasingly focusing on how existing medicines, licensed for use in treating specified conditions, can be investigated for use in treating other conditions. However, where these medicines are off-patent, the current commercial incentive for pharmaceutical companies is often too small to encourage them to seek a licence for use in treating these other conditions. Whilst medicines can be, and are, prescribed off-label there are a number of barriers to this happening in a timely way for alternative uses that are not included in the marketing authorisation. Included in these barriers is that healthcare professionals are not all familiar with the conditions for appropriate

off-label prescription and there is a lack of a systematic mechanism for scrutinising and reaching a view on evidence. Annex B includes *'Evidence from charities'* which provides further details of some barriers to repurposing.

2.6 Such barriers and many related issues were highlighted to the Government in 2014 and 2015 in the form of two Private Member's Bills, both called the 'Off-patent Drugs Bill.' The Bills would have required the Government to seek licences for off-patent drugs when there was evidence that they could be clinically effective and safe for a new purpose, and when no pharmaceutical company had sought a licence. They also intended to require these drugs to be referred to NICE for a technology appraisal (TA) which, if positive, would give the NHS a legal obligation to fund them.

2.7 The Bills were strongly supported by many medical research charities and professional associations. Those who supported the Bills cited the examples of tamoxifen and a group of drugs, bisphosphonates, to make their case. Bisphosphonates are primarily used to prevent or treat osteoporosis, but some evidence has shown that the drugs could also help women treated for early breast cancer, after the menopause, to reduce the risk of the cancer spreading to the bone.[4] Evidence also suggests that tamoxifen, used to treat breast cancer, could be used to help prevent breast cancer in people who have a strong genetic pre-disposition to develop it.

2.8 The Government's response to the Bills was to work collaboratively with medical research charities and other stakeholders to identify barriers and examine, in the first instance, where matters could be improved to mitigate barriers to help ensure patients received the care they need. A task and finish group – the Drug Repurposing Group - was established whose membership is listed in Annex A of this report. Efforts at this stage **resulted in the development of a GMC guide[5] to support prescribers as well as strengthening NICE systems to support NHS medicines use.**

2.9 The Group's focus then turned to ensuring that the benefits of medical research can be better translated into practice to help improve patient outcomes. This highlighted the need for a mechanism to enable the adoption of off-patent medicines, for which there is robust evidence of effectiveness in treating new conditions, to be used in the NHS. Medical research charities and NICE have led the design and development of this framework, referred to as the '**drug repurposing framework'** in this report**.**

2.10 The group has looked at, and tested, ways in which medical research charities can work with MHRA and the British Generic Manufacturers Association (BGMA) to pursue a licensing route. This has included receiving scientific advice from MHRA experts and, separately, proposals for a tax credit or a catalyst fund to support the work that would be needed by industry. The group has also produced the drug repurposing framework; providing a route for research into new uses for existing drugs to be incorporated into clinical

[4] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2815%2960908-4/fulltext
[5] Available at http://www.gmc-uk.org/guidance/28349.asp

practice. This report presents the development of the framework to date and explains how it relates to two off-patent, repurposed drugs.

2.11 The report includes a number of recommendations. The first recommendations present different ways in which sponsors can work with MHRA to pursue a licensing route. The report also makes recommendations to develop financial incentives that would encourage generic manufacturers to participate in drug repurposing and a mechanism of testing the drug repurposing framework.

3. BACKGROUND

3.1 Drugs have been repurposed for many years but the term “drug-repurposing” is fairly new to many. Some drugs in common use today have been repurposed; for example, aspirin began as a medicine for pain relief, though is now more commonly used in the management of coronary heart disease.

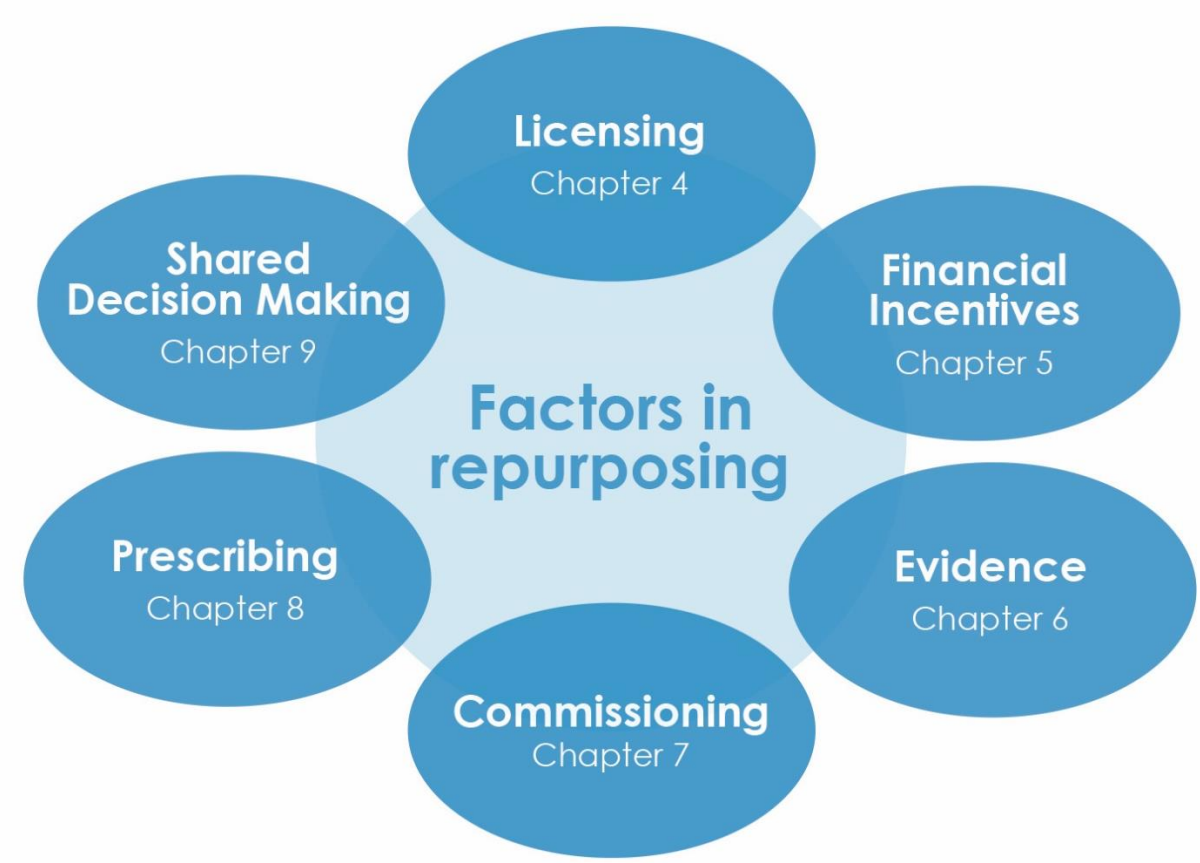
3.2 Drug repurposing occurs when new evidence is established about a drug demonstrating that it can be useful for a condition for which it was not originally developed. The spectrum of change in use is relatively wide. A new use can be very close to the original, for example, using a drug for prostate cancer for the same condition but earlier in the treatment pathway. A new use can also be in quite a different disease group from the original, for example, research into the use of diabetes drugs for Parkinson’s disease.

3.3 Interest in repurposing drugs is growing, particularly as we expand our knowledge about human and disease biology, and better understanding how existing drugs work. This interest is reinforced as new drug development becomes more challenging, less expensive treatments are sought, and research technology and innovation advance. This is an area where the UK has considerable expertise already and which is ripe for further development. The Government response to the Accelerated Access Review, *Making a reality of the Accelerated Access Review*, states that repurposed medicines, where a new indication is found for an existing product, will be eligible to benefit from the Accelerated Access Pathway (AAP). The AAP aims to get transformative products into the NHS as quickly as possible by streamlining regulatory and market access decisions.

3.4 Those who are interested in drug repurposing come to it from a number of directions. Pharmaceutical companies are incentivised to research and develop new uses for drugs if they effectively protect that investment whilst medicines are within patent and medicines legislation exclusivity periods. However, this is not the case if they are outside these periods. This is a growing area. For some off-patent drugs, medical research charities and academic researchers are active in commissioning research and exploring new uses. The Drug Repurposing Group has worked with stakeholders in each area, receiving the most input from the medical research charities and academic researchers with a focus on off-patent drugs.

3.5 The diagram (*Figure 1)* sets out the factors that need to be considered in repurposing. They are not sequential. Medicines licensing examines the safety, efficacy and quality of a medicine. Other factors, such as commissioning, prescriber responsibilities and patient choice, determine patient access. The starting point for anyone working in this area will depend on the work that has already been done and the role they intend to take in repurposing.

Figure 1: **Factors in repurposing**



3.6 The following chapters cover each of the factors in turn giving information about current systems and making proposals for future developments.

4. LICENSING

This chapter describes current routes to licensing and how they support drug repurposing.

4.1 The medicines regulatory framework can support the process to follow a licensing route. The licensing system should be the primary route to repurposing when establishing a new indication.

4.2 The majority of medicines used by the NHS are generics, drugs for which the patents and periods of data and marketing exclusivity of the originator product have expired. In 2016, 77.7% of medicines used by the NHS were generics[6]:

> *'A generic medicine is a medicine that is developed to be the same as a medicine that has already been authorised (the 'reference medicine'). A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s) as the reference medicine. However, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine.' (European Medicines Agency 22 November 2012 EMA/393905/2006 Rev. 2)*

4.3 Generic medicines are usually interchangeable, nearly always lower cost versions of the originator medicine and their use saves the NHS about £13 billion[7] every year. Originator and generic medicines use the same system of licensing, regulated by the Department of Health (DH) through the MHRA.

The current licensing system

4.4 The licensing system ensures that patients receive medicines that have been scientifically assessed to meet published European standards of safety, efficacy and quality. These standards are applied and enforced in the UK by MHRA. MHRA carries out its work in the licensing of medicines by assessing applications against the scientific standards laid out in European guidelines, other regulatory legislation and the UK Human Medicines Regulations 2012 Act (as amended). UK public health is further protected by post-marketing surveillance (including post-licensing safety monitoring – pharmacovigilance), performed by the company marketing the product and then reviewed by MHRA. The UK regulatory system is further reinforced by a system of MHRA inspections, for example, of manufacturing sites, in the UK and globally.

[6] NHS Digital, Prescriptions Dispensed in the Community England 2006 to 2016, published 29 June 2017
[7] NHS Digital, Prescriptions Dispensed in the Community England 2006 to 2016, Table A6 in the Appendix Tables, published 29 June 2017

4.5 A licensed medicine includes approved information for healthcare professionals (Summary of Product Characteristics - SmPC) and for patients (Patient Information Leaflet - PIL). This information summarises the approved uses (licensed indications), dosage, warnings, known adverse effects and interactions with other medicines and foods. The PIL is provided with each packet of the medicine and helps the patient to understand how to use the medicine as intended by the prescriber, including information on any risks associated with use of the medicine.

4.6 Although the medicines licensing system is open to all, in practice it is almost exclusively used by pharmaceutical companies, who have the necessary infrastructure and expertise to navigate the system and satisfy its requirements. The responsibilities of a Marketing Authorisation Holder (MAH) are continuous and include lifecycle maintenance, keeping up to date with regulatory science, monitoring safety (including off-label use), being subject to MHRA inspections and having designated staff with legal responsibilities. Additionally, the MAH is responsible for keeping the information in the PIL and SmPC up-to-date to inform patients and healthcare professionals about how to use the medicine in the licensed setting. **There is no legal barrier to a medical research charity or academic unit becoming a MAH if it wishes to make arrangements to fulfil the necessary requirements, either independently or through partnership arrangements with an existing MAH or a range of contract service providers.**

4.7 Generic medicines already approved by MHRA can be used as a starting point for the introduction of repurposed medicines, through the licensing route, by a relatively simple, quick process. This approach makes best use of existing infrastructure. The generic medicine has already been licensed by MHRA. It is being routinely manufactured and supplied to the NHS with its quality and safety continuously monitored. All generic medicines have a well-established safety (pharmacovigilance) profile in their existing licensed indications.

Routes to licensing

4.8 Licensing is the first choice for bringing repurposed medicines into routine clinical use in the NHS.

4.9 When considering the licensing route for a repurposed medicine, there are three important areas of **assistance available from MHRA** for medical research charities, academic researchers and other stakeholders:

i. **MHRA Innovation office** – provides a single point of access to expert regulatory information, advice and guidance that helps organisations of all backgrounds and sizes develop innovative medicines. Further information is available here.

ii. **Clinical trial protocol advice** – helps researchers and clinical investigators design their studies in a way that is most likely to meet MHRA licensing requirements.

iii. **MHRA scientific advice** – this provides opportunities for researchers to discuss their plans and progress at various milestones as they gather data during the clinical programme. Joint scientific advice from the MHRA and NICE is also available allowing consideration of the evidence needs for licensing and demonstrating clinical and cost-effectiveness compared to current treatment options. Further information is available here.

4.10 For those researchers with an interest in gaining a licence in other European countries, in addition to the UK, assistance is also available from the European Medicines Agency (EMA) office for Small & Medium Size Enterprises (SME). Information is available here.

4.11 Scientific advice meetings are a mechanism to improve communications between drug developers and regulators during the drug development process. While standard practice for industry, the benefits provided by these meetings are under-utilised by academia and medical research charities. For medicines repurposing, MHRA scientific advice meetings can:

i. Provide guidance on clinical study protocols to help improve them before they start;

ii. Review study programmes as they progress for licensing suitability; and

iii. Advise on suitability of proposed studies and on key data to be collected, so supporting efficient product development.

4.12 As part of the programme of work to establish more effective pathways into routine clinical practice for repurposed drugs, two medical research charities took MHRA scientific advice in early 2017:

i. Breast Cancer Now – bisphosphonates to prevent breast cancer recurrence; and
ii. Anticancer Fund – propranolol in the treatment of angiosarcoma, a rare soft tissue sarcoma.

4.13 For these two examples, it has been demonstrated that it would be possible to apply for a licence, with a relatively small amount of additional work, most of which was already planned.

4.14 The charities found the experience extremely useful,[8] with MHRA providing practical focused feedback on the levels of evidence required to license the new uses. Seeking and following MHRA scientific advice at an early stage of development helps ensure clinical research programmes are designed in a way that supports achieving licensing. At the same time, this reduces the risk

[8] Pantziarka P (2017) Scientific advice - is drug repurposing missing a trick? Nature reviews. Clinical oncology, 14(8), pp. 455–456. http://www.nature.com/nrclinonc/journal/v14/n8/full/nrclinonc.2017.69.html

of studies that result in limited evidence for an otherwise promising treatment option.

4.15 When considering the licensing route and engagement with MHRA, medical research charities and academics can obtain advice and support from bodies such as the Association of Medical Research Charities, the Association of the British Pharmaceutical Industry (for general policy guidance only), the British Generics Manufacturers Association or specialist regulatory consultants who operate in the field.

4.16 At present, there are three main routes for licensing a new medicine, to make it available for use in the NHS. The assessment is on the basis of its quality, safety and efficacy, notwithstanding the health technology assessments of cost-effectiveness that may follow.

i. National route – a UK only procedure, operated by MHRA
ii. Decentralised procedure, DCP (and Mutual Recognition Procedure, MRP) – European procedures, operated by MHRA and other EU regulatory agencies working in cooperation. The outcome is a UK national licence and companies can also obtain authorisations in other Member States they choose using the same data package.
iii. Centralised Procedure – operated by the EMA, resulting in a single pan-European approval covering all EU countries.

4.17 DCP, MRP and Centralised Procedure are used by pharmaceutical companies that wish to market their product in more than one European country.

4.18 The licensing of a medicine by MHRA or the EMA gives assurance to patients, prescribers and other stakeholders that the medicinal claims for the medicine are supported by strong evidence that has been assessed against an independent standard.

4.19 After a generic medicine has been licensed, changes to it can be made by the licence holder submitting a variation application. This can include a clinical variation to add a new indication (medicinal use), which would be the case for a repurposed medicine. Net assessment time for clinical variations is typically about six months from submission to approval. This illustrates that adding the clinical evidence available to medical research charities (by way of a clinical variation) to an existing generic medicine would be a rapid way to implement the evidence for a repurposed drug, and make it available to patients.

4.20 The licensing route for adding a repurposed indication to an existing generic medicine has the benefit of using existing, well established MHRA processes following a short, predictable timetable.

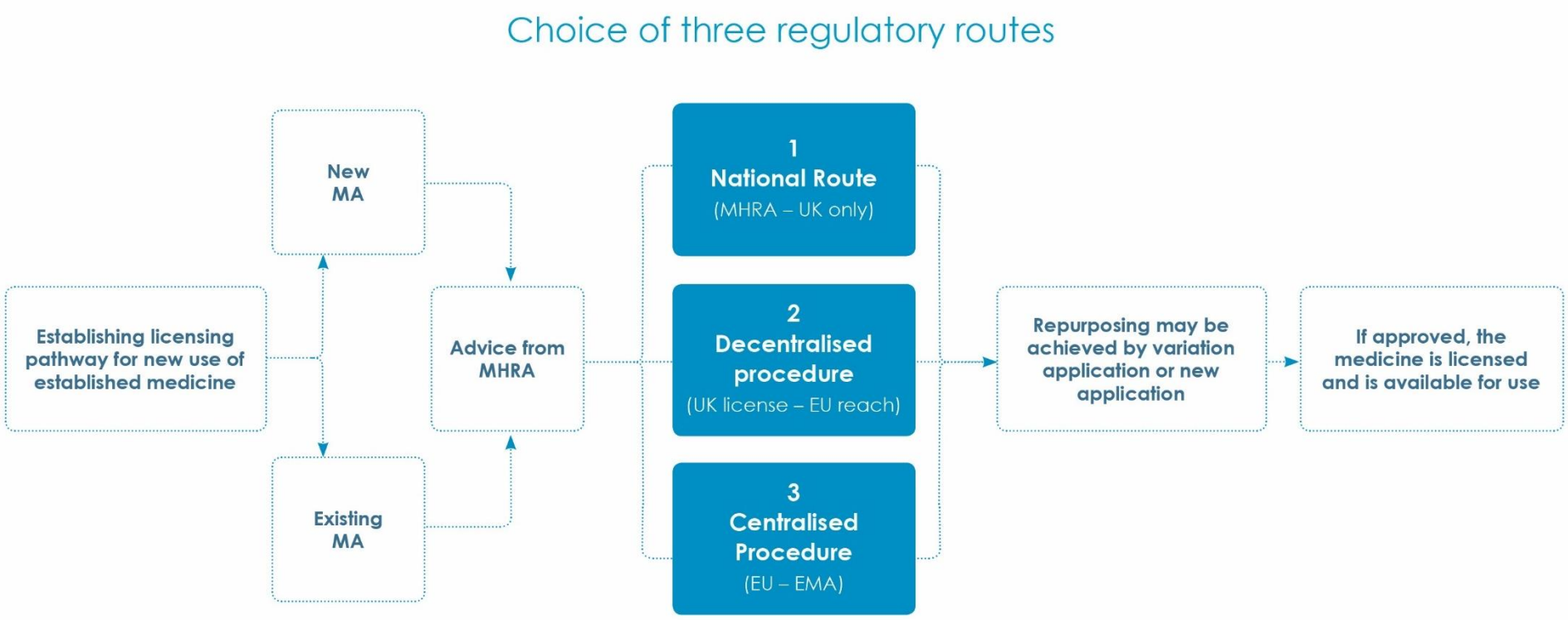
4.21 The addition of the repurposed indication, with details of the indication, dose and any safety implications, would be communicated to health professionals and patients in updated clinical particulars in the SmPC and PIL.

4.22 The information and data that has to be included in a clinical variation application are laid out by MHRA here.

4.23 Once approved, the Licence Holder is required to maintain the licence. This includes updating the patient information relating to the medicine and ensuring continuous safety monitoring. The licensed uses of the medicine may be advertised to healthcare professionals (prescription only products) or to the public (non-prescription products). Advertising of medicines is also regulated by MHRA.

4.24 Figure 2 illustrates the licensing pathway to be followed for an established, generic medicine.

Figure 2: Licensing Pathway



Establishing licensing

- Any organisation can become a marketing authorisation holder (MAH)
- The Sponsor will need to fulfil the necessary requirements either independently or through partnership arrangements with an existing MAH or range of contract service providers
- Process of repurposing an existing licensed, generic medicine is relatively simple and quick

Advice from MHRA

- MHRA Innovation Office provides a single point of access to expert advice
- MHRA can also advise on clinical trials and broader licensing support (via scientific advice)

Clinical variation

- Regardless of the pathway, the appropriate application for establishing a new licensed indication may involve a variation application
- A clinical variation application takes about 6 months from submission to approval. Added clinical evidence to an existing generic medicine supports that variation

Approved license

- Once licensed, the medicine and its new indication can then be incorporated into the established drug safety monitoring and regulatory review processes
- The new indication can then be communicated to healthcare professionals and patients in updated guidelines and NICE reviews
- The medicine can then be incorporated into NHS commissioning and care pathways, as appropriate

5. FINANCIAL INCENTIVES

This chapter discusses financial incentives and makes proposals for the future.

Bringing together clinical evidence available to medical research charities for a repurposed drug with generic medicine manufacturers

5.1 At present there is no meaningful financial incentive for generic medicine manufacturers to participate in medicines repurposing. Once a generic market is formed after patent expiry of the originator medicine, price competition between multiple suppliers nearly always leads to very rapid price decline. Subsequently, a commodity market operates based on price, availability and supply chain competition. Therefore, the profitability of an individual generic medicine is not large enough to support any new R&D investment (including the costs of licensing) such as a repurposed indication. If one generic medicine manufacturer licenses the new indication, the benefit from increased prescribing would be enjoyed by all MA holders. This is due to the very high levels of generic prescribing in the UK, plus interchangeability between generic suppliers at the point of dispensing. Even if prescribing volumes increased significantly this would provide little financial reward for generic manufacturers due to the commodity nature of the market, with intense price competition between manufacturers. Therefore, there is currently no financial incentive for one manufacturer to lead the way by licensing a repurposed medicine.

5.2 Developing a partnership model linking generic medicine manufacturers (contributing a market authorisation (MA), already available product & pharmacovigilance) with medical research charities (contributing disease-specific expertise, demonstrated unmet patient need, and human resource) and academics (contributing clinical and scientific expertise plus data) would create a licensing route for the repurposing of medicines. This partnership model maximises the use of existing capabilities, infrastructure and processes.

CURRENT INCENTIVES

Orphan drug designation

5.3 This is a European level scheme administered by the European Medicines Agency (EMA) for conditions with a low incidence and unmet clinical need. A drug must meet certain requirements in order to qualify for orphan designation:

- it must be intended for the treatment, prevention or diagnosis of a disease that is **life-threatening** or **chronically debilitating**;

- either -
  - the **prevalence** of the condition in the EU must not be more than five in 10,000, or

- it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and

- no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of **significant benefit** to those affected by the condition.

5.4 EMA orphan drug designation provides a range of incentives, most significantly 10 years of market exclusivity. Details are available here.

5.5 A few repurposed medicines may fall within the orphan category. Further information on this is available here. There is also a scheme to incentivise development of paediatric medicines known as PUMA – Paediatric Use Marketing Authorisation. Information is available here.

The Patent Box

5.6 The Patent Box enables companies to apply a lower rate of Corporation Tax (10%) to profits earned from its patented inventions. Details are available here.

5.7 In addition to recognising patented inventions, the Patent Box also gives the tax reduction to products that have obtained exclusivity through MHRA/EMA regulatory decisions such as paediatric use and orphan medicinal products. Details of this are available here.

5.8 The same tax reduction could be applied to companies that license repurposed drugs outside their patent protection period. To follow this route, the partnering medical research charity or academic would need to be willing for their data to be used exclusively by one pharmaceutical company.

5.9 This is generally unlikely and would probably lead to case by case considerations that balance achieving licensed repurposing along with providing commercial exclusivity to one company. Additional complexity would also arise in the frequent situations where the clinical data has been funded by several parties, such as the charity, NIHR, Research Councils and academic groups. For these reasons, the Patent Box is not the preferred option for drug repurposing.

FUTURE INCENTIVES

Possible new incentive mechanisms

5.10 The financial incentives, for R&D, that are already in place were not designed with drug repurposing specifically in mind. Therefore, although they can be helpful, a more tailored approach is needed.

5.11 Two main potential routes exist to provide a generic company with a meaningful financial incentive. One is through the price of the product. This

could be achieved either under reimbursement arrangements for generic medicines e.g. Category M or by the company applying a brand name (to link prescribing and dispensing). However, significantly increasing the price of the medicine is not desirable for the NHS or for patients. Using an indirect incentive mechanism would limit both direct impact on the cost of medicines and the overall patient treatment cost.

5.12 A second option is for the company to be incentivised and rewarded in a way which is not connected to product price is via Research & Development Tax Credits. Details of this are available here. This would require the scope of the existing scheme, for SMEs, (as defined in guidance documentation) to be expanded to include the repurposing of generic medicines. The R&D Tax Credit guidance documentation is regularly updated, usually several times a year. Therefore, this is a well-established mechanism.

5.13 The amount of R&D tax relief available is the actual amount spent multiplied by 230% (or 130%). Eligibility is currently defined as:

"Your company can only claim for R&D tax relief if an R&D project seeks to achieve an advance *in overall knowledge or capability in a field of science or technology through the resolution of scientific or technological* uncertainty *- and not simply an advance in its own state of knowledge or capability.*

The project must relate to your company's trade - either an existing one, or one that you intend to start up based on the results of the R&D"

Eligibility guidance is given in detail by HM Revenue and Customs (HMRC) here.

5.14 It would need to be agreed by HMRC and government that participation by generic pharmaceutical manufacturers in medicines repurposing is eligible R&D to benefit from the tax credits. To do that, the range of eligible activities would need to be agreed. This could then be implemented through an update to the eligibility guidance. Legislative changes would not be needed.

What activities and investment would a generic manufacturer contribute?

5.15 This list is not exhaustive, but includes the following:

i. Preparation and conduct of MHRA scientific advice meeting
ii. Supplementing clinical data, if required by MHRA, by the company performing and funding additional clinical trials
iii. MHRA fees
iv. Preparation and submission of clinical variation
v. Regulatory dossier preparation
vi. Answering MHRA requests for additional information
vii. Product specific pharmacovigilance and Risk Management Plan (RMP)
viii. Updating product information with the new indication

5.16 Since these activities may extend beyond 12 months, eligibility for R&D tax relief should be available across several years. The scope would not include the clinical data, other expertise, and resources made available by the medical research charity.

5.17 The level of investment by a generic medicines manufacturer is likely to be in the region of hundreds of thousands of pounds. Larger costs would only arise if MHRA required significantly more clinical data than that already provided by the partnering medical research charity.

An independent fund

5.18 Another financial incentive option could be for Government to establish a special fund of several million pounds over, for example, a three-year period to support the repurposing of medicines. During this period of time, longer term incentive mechanisms could be established. A UK catalyst fund would help establish the UK as a global leader in medicines repurposing. Access to the fund could be limited to generic manufacturers who are SMEs and/or local manufacturers, as part of the sector deal for the UK's Life Sciences Industrial Strategy. It would complement the arrangements set out in the government response to the Accelerated Access Review, "*Making a reality of the Accelerated Access Review"*, which states that repurposed medicines will be eligible to benefit from the Accelerated Access Pathway. The Pathway aims to get transformative products into the NHS as quickly as possible by streamlining regulatory and market access decisions.

5.19 Putting in place a process with modest financial incentives to support the repurposing of generic medicines will deliver significant benefits to the UK health economy. This can be achieved primarily through adapting and reconfiguring existing systems, thereby maximising predictable outcomes, with a level of investment that can be closely monitored and controlled. Developing an innovation pathway using generic medicines, to address unmet clinical need, would be a cost-effective option, adding to those already provided by breakthrough patent protected medicines and other medical innovations.

5.20 The amount of financial incentive made available to generic manufacturers could be at two levels, with a higher rate being available for new repurposed clinical indications where no other medicines are licensed.

6. EVIDENCE

6.1 Good quality healthcare relies on the use of reliable, robust and up-to-date evidence. High quality research produces evidence that can be used to deliver care. The pharmaceutical industry, medical research charities and academic institutions all play a key part in identifying and pursuing research into new treatment options and approaches. Medical research charities also explore other areas including the use of off-patent medicines in new indications. Academic institutions support research across the spectrum of activity.

6.2 NICE provides the NHS and those who rely on it for their care with an expanding range of advice on effective, good value healthcare. NICE have gained a reputation for rigour, independence and objectivity. Increasingly the full range of evidence can be accessed through the NICE Evidence portal.

Surveillance systems

6.3 The Commission on Human Medicines (CHM) is an advisory non-departmental body which advises ministers on the safety, efficacy and quality of medicinal products.

6.4 CHM has arranged to share meeting agendas with NICE whilst NICE has an open invitation to attend CHM meetings. Such arrangements are important mechanisms to support NICE's medicines surveillance systems.

6.5 NICE and MHRA hold quarterly meetings to identify and address areas of mutual interest. Repurposed drugs have been a standing item in these meetings.

NICE guidance and advice

6.6 The production of NICE guidance is led by the evidence supporting the use of a particular medicine for a particular condition. If there is sufficient, robust evidence for the safety and cost-effectiveness of a medicine then NICE may recommend the use of that medicine.

6.7 NICE continues to develop and adapt its methods to enable robust guidance on the off-label use of medicines, where this is in-line with the best available evidence. The NICE charter explains the approach. Action has been taken in many areas to improve information flows from NICE to clinicians and make clearer the routes for information to reach NICE from patient and research communities.

NICE evidence summaries

6.8 NICE evidence summaries provide a summary of the best available evidence for selected medicines that are considered to be of significance to the NHS. Topics include new medicines (where a medicine has been recently launched in the UK) or unlicensed medicines/off-label use of licensed medicines when

there is no licensed medicine appropriate for a significant proportion of people needing treatment for a condition. Topics are only considered where there is no existing NICE guidance available.

6.9 NICE are commissioned by NHS England to produce evidence summaries to inform commissioning policies (*see also chapter 7*). Further information on NHS evidence summaries is here.

NICE medicines and prescribing associates network

6.10 Once NICE has made a recommendation in its guidance or advised on the off-label use of a medicine, it is incorporated into NICE's education programme for NICE's medicines and prescribing associates network.

6.11 NICE routinely works with a community of over 70 associates, who are clinicians from a range of disciplines. These associates support and promote high quality, safe, cost-effective prescribing and medicines optimisation, within local health economies.

6.12 Associates work with their own organisation and their local health economy to:

- Support the adoption of NICE and other high-quality guidance into practice
- Improve safety through highlighting issues of medicines safety, risk and 'never events'
- Support the local introduction of new medicines
- Develop leadership, facilitation, decision-making and management skills

Medicines awareness

6.13 NICE produces a summary and commentary on important new evidence as part of its Medicines Awareness Service. As a relevant example to the drug repurposing work, in November 2015, NICE published the medicines evidence commentary 'Early breast cancer: adjuvant bisphosphonates treatment beneficial in postmenopausal women,' providing the NHS with important new evidence that could help signal a change in clinical practice. Important new evidence therefore covers unlicensed and off-label medicine use, and this is sent not only to associates (and therefore widely through their networks) but also to a network of clinical pharmacologists/educators and to the BNF to be integrated into its content development process (*see section 6.16*).

6.14 NICE routinely shares medicines evidence commentaries with over 10,000 prescribers and pharmacists and alerts over 11,000 clinicians whose practice involves commissioning, managing, prescribing or administering medicines.

British National Formulary (BNF)

6.15 NICE manages the contract to provide the BNF to prescribers in England and works closely with the publisher to maintain quality and consistency with national policy and guidance. The BNF is a pharmaceutical reference book which provides information about medicines available in the UK, including indications, contraindications, side effects, doses and price.

6.16 As part of the group's work, the BNF has reviewed around 200 off-label indications that are included in clinical guidelines and will add to the Formulary those that meet the necessary evidence criteria. This work is expected to be complete by the end of 2017. Moving forward, the BNF will continue to review off-label uses of medicines included in clinical guidelines, as and when they arise. The BNF has also developed an approach to presenting off-label medicines in a standard way to help clinicians, which is currently being implemented.

Specialist Pharmacy Service (SPS)

6.17 The NHS Specialised Pharmacy Service (SPS) is commissioned by NHS England to support services and healthcare professionals by offering expert help and advice about all aspects of medicines usage. This covers the delivery of evidence based information in response to enquiries as well as medicines preparation and medicines procurement. The individual service elements which make up SPS include medicines information, medicines use and safety, quality assurance and procurement. The SPS is responsible for the operational functions of the Regional Medicines Optimisation Committee (RMOC) through the provision of the professional secretariat on behalf of NHS England.

7. COMMISSIONING

This chapter describes how the NHS chooses what to routinely commission based on the best available evidence.

7.1 In specific circumstances, off-label use of a medicine is an appropriate treatment option and can be commissioned for use. Better access would be achieved by enabling a recommendation to be made on the commissioning of off-patent repurposed medicines for use in the NHS, thus facilitating their availability for clinicians and patients.

7.2 In England, local Clinical Commissioning Groups (CCGs) commission hospital and some community services and work with GPs to organise local primary care. The majority of public health services are commissioned locally by Public Health England along with local authorities. NHS England has over-arching commissioning responsibilities for primary care and commissions highly specialised care, e.g. organ transplantation; the latter is known as specialised commissioning.

7.3 The Regional Medicines Optimisation Committee (RMOC) established by NHS England in 2017 has a remit in relation to repurposed drugs. It would be appropriate for an application to be made to the RMOC for consideration of a repurposed medicine where it is likely to be used widely in a specific patient cohort. In this circumstance the RMOC would consider the repurposed medicines in line with its published operating model and (supported by the NHS Specialist Pharmacy Service and NICE) assess the available evidence. The RMOC would issue national advice to CCGs on the use of the off-patent repurposed medicine.

7.4 In circumstances where NHS England is the responsible commissioner, i.e. for specialised commissioning, the NHS England specialised commissioning team would produce a clinical commissioning policy. One such example of this is, docetaxel chemotherapy, an off-patent, off-label medicine for use earlier in the treatment pathway for men with advanced prostate cancer (*see annex D*).

7.5 For a repurposed medicine to be considered by a CCG, RMOC or NHSE for commissioning[9] it would have to fulfil all the following criteria:

- The medicine is off-patent (see definition for ‘off-patent medicine’);
- The formulation is currently licensed in the UK for a particular therapeutic indication(s);
- There is no licenced medicine available for the indication being considered; and

[9] These are criteria for commissioning review. However, any off-label use of a medicine remains the responsibility, liability and decision of the prescriber and the dispensing pharmacist, in discussion with the patient. The prescribing hierarchy is more fully described in Chapter 8 and is not superseded by commissioning advice.

- A robust body of evidence (efficacy and safety data) is available to demonstrate that the benefit/risk evaluation is positive in the new indication, which is considered to be 'practice-changing' (see below). The evidence contains sufficient information for a health practitioner to take clinical responsibility for its use and to have an informed benefit/risk discussion with a patient. There is a compelling reason why licensing is not possible for the new indication.

What is meant by practice-changing research?

7.6 What is considered 'practice changing research' can vary depending on the treatment and disease area in question and will need addressing on a case by case basis.

7.7 The intention is that the level of evidence to inform a commissioning policy or advice statement would normally be of a similar standard to that used for licensing. For instance, this would typically involve including a well-conducted phase 3 randomised, controlled clinical trial or meta-analysis of these. This would provide assurances for patients, prescribers and other stakeholders on the safety and efficacy of the medicine in its new indication.

7.8 This can vary depending on the treatment and disease area in question and will need to be assessed on a case-by-case basis. The relevant clinical community is best placed to decide whether research is 'practice changing'.

7.9 Requests for access to any drug in advance of completion of a relevant clinical trial are a matter for the patient and clinician, and fall outside the remit of this report.

Description of the drug repurposing framework

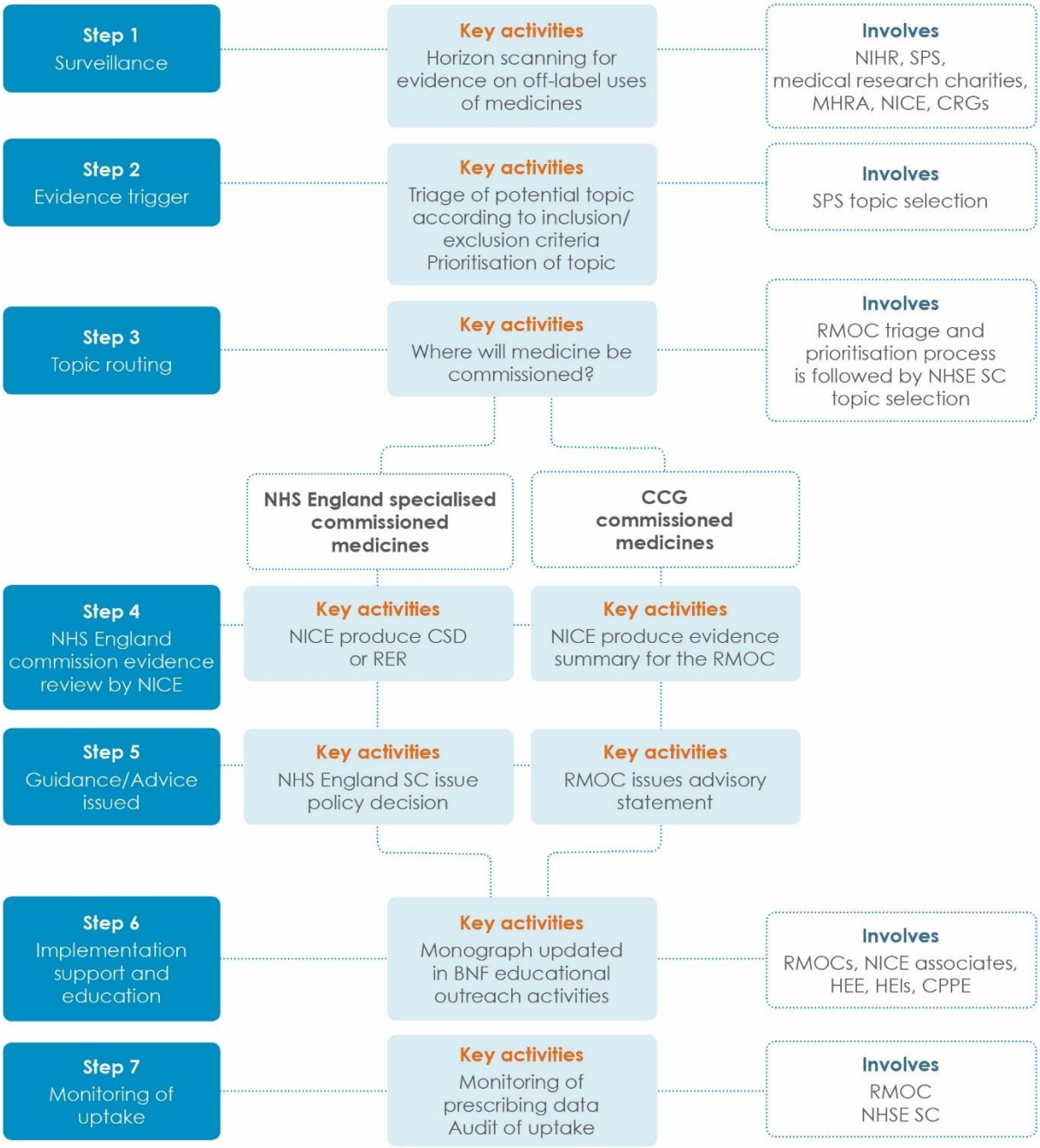
7.10 Before accessing the mechanisms described in the framework, it is likely that a proposed new indication would already have been through several stages. The existing evidence base will have been reviewed (*see Step 4 of the framework*) in the proposed repurposed indication, and which has resulted in a robust body of evidence, which is considered 'practice-changing research'. This would generally require input from several different parties, including patients, disease experts, study design experts, and development/regulatory experts. Where necessary, MHRA will have given scientific advice on aspects within its areas of regulation (efficacy, safety, quality).

7.11 The framework is not intended as an early access scheme. An indication could be pursued through the system if it is likely to remain off-label. The framework should not be used to make indications available, which are in the process of being licensed and are only temporarily off-label.

7.12 The framework draws on what we know currently about the developing role of the Regional Medicines Optimisation Committee. It will evolve further as the Committee develops its programme of work. The following paragraphs give more information on the steps set out in the framework diagram (*Figure 3)*.

Figure 3:

Framework to improve access to repurposed medicines for patients



NHSE SC: NHS England Specialised Commissioning
SPS: Specialist Pharmacy Services
NIHR: National Institute for Health Research
CRGs: Clinical Reference Groups
CCGs: Clinical Commissioning Groups
CSD: Commissioning Support Document
RMOCs: Regional Medicines Optimisation Committees
MOPP: Medicines Optimisation Priorities Panel
BNF: British National Formulary
HEE: Health Education England
HEIs: Higher Education Institutions
CPPE: Centre for Pharmacy Postgraduate Education
RER: Rapid Evidence Review
APC: Area Prescribing Committee

Step 1 – Surveillance

7.13 NICE is alerted to evidence through surveillance processes. Surveillance for new evidence on the off-label use of a medicine includes looking at suggestions from the service, patient groups, NIHR horizon scanning and Clinical Reference Groups (CRGs). This is co-ordinated by Specialist Pharmacy Services (SPS) as part of the provision of RMOC secretariat support.

Step 2 – Evidence trigger

7.14 NICE, SPS and NHS England review the evidence identified against published inclusion and exclusion criteria (*see section 7.5*).

7.15 **The BNF is notified to the new evidence:** The BNF is notified of the evidence supporting the new use of an approved medicinal product, with a view to it being included in the BNF. Using their own processes, the BNF include information on off-label use of an approved medicinal product if they are satisfied with the supporting evidence.

Step 3 – Topic routing

7.16 **A decision on the appropriate commissioning body is made:** This step will need to be considered in tandem with the previous step as it has a direct impact upon who undertakes the assessment that follows. At this stage, NICE and NHS England must decide who is responsible for commissioning the indication – either CCGs or NHS England Specialised Services (NHSE SC). NHS Clinical Commissioners (NHS CC) are included in the decision-making process. In broad terms, the commissioner of the repurposed medicine will ordinarily commission medicines in the disease area for which the off-label medicine is indicated.

7.17 **The role of CCGs when they are responsible for commissioning:** In accordance with the operating principles of the RMOCs, stakeholders can also make a proposal directly to the RMOCs. At this stage the request will be triaged and if the request passes this process it will be passed to the Medicines Optimisation Priorities Panel (MOPP) of the RMOC. The MOPP will confirm the suitability of the topic for consideration by the RMOC and assign the topic to the RMOC workplan.

Step 4 – NHSE commission evidence review

7.18 The assessment process is undertaken. The evidence reviews cover effectiveness, safety, patient factors and resource impact.

7.19 **Commissioned by Specialised Services:** NICE or another evidence provider may be commissioned to undertake an evidence summary of the medicine, but may not do so on every occasion.

7.20 **Commissioned by CCGs:** NICE or another evidence provider may be commissioned to undertake an evidence summary of the medicine but may not do so on every occasion.

Step 5 – Guidance/Advice issued

7.21 **Commissioned by Specialised Services:** The commissioning policy is communicated to all relevant health practitioners in the NHS, including the relevant NHS England Clinical Reference Group(s).

7.22 **Commissioned by CCGs:** The prescribing recommendation is communicated to the most relevant area specialist in all CCGs.

Step 6 – Implementation support and education

7.23 Local CCG networks, e.g. Area Prescribing Committees (APCs), will pick up the advice and use existing mechanisms to support prescribers (*see section 1.2*) in considering their decision regarding implementation. They will also support shared decision-making between prescriber and patient. Normal continuing professional development activity will support prescribers in learning about the new indications, as required. If appropriate, an updated monograph will be published in the BNF. Commissioning Support Documents (CSD) will support implementation in specialised commissioning.

Step 7 – Monitoring of uptake

7.24 The ultimate goal is better informed decision-making and to facilitate timely access to repurposed medicines for patients. This is the outcome on which the framework and its use must be measured using prescribing data and metrics. Consideration may be given to inclusion in the medicines optimisation dashboard and monitoring for variation in practice by the NHS England RightCare programme.

8. PRESCRIBING

8.1 Prescribers can prescribe medicines outside their licensed indications where it is clinically appropriate. Examples include instances where the medicine has not been licensed for the patient group concerned, as is the case with many drugs that are used for children which have not historically been tested on children. It may also be the case where the licensed drug does not suit the individual patient, perhaps due to allergies or because of reactions to another medicine they are taking. In these circumstances, using an alternative licensed medicine off-label may be the best clinical choice for that patient.

8.2 The General Medical Council (GMC) provides guidance to doctors on when it is suitable to prescribe a medicine that has not been granted an MA by MHRA, i.e. an unlicensed medicine, and when it is appropriate to prescribe a medicine with an MA for a clinical use that has not been approved by MHRA, i.e. an off-label medicine. Such guidance is available on the GMC website here. **This guidance reads:**

GMC Guidance – Responsibilities for prescribing medicines other than in accordance with its licence

You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.

69. Prescribing unlicensed medicines may be necessary where:
a. There is no suitably licensed medicine that will meet the patient's need.

Examples include (but are not limited to), for example, where
i. there is no licensed medicine applicable to the particular patient. For example, if the patient is a child and a medicine licensed only for adult patients would meet the needs of the child; or
ii. a medicine licensed to treat a condition or symptom in children would nonetheless not meet the specific assessed needs of the particular child patient, but a medicine licensed for the same condition or symptom in adults would do so; or
iii. the dosage specified for a licensed medicine would not meet the patient's need; or
iv. the patient needs a medicine in a formulation that is not specified in an applicable licence.
b. Or where a suitably licensed medicine that would meet the patient's need is not available. This may arise where, for example, there is a temporary shortage in supply; or
c. The prescribing forms part of a properly approved research project.

70. When prescribing an unlicensed medicine you must:

a. be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy
b. take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so
c. make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine.'

71. You must give patients (or their parents or carers) sufficient information about the medicines you propose to prescribe to allow them to make an informed decision.

72. Some medicines are routinely used outside the terms of their licence, for example in treating children. In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the licence. In other cases, where prescribing unlicensed medicines is supported by authoritative clinical guidance, it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population. You must always answer questions from patients (or their parents or carers) about medicines fully and honestly.

73. If you intend to prescribe unlicensed medicines where that is not routine or if there are suitably licensed alternatives available, you should explain this to the patient, and your reasons for doing so.

GMC Hot Topics

8.3 In 2015 the General Medical Council (GMC) presented the issue of off-label prescribing as a 'Hot Topic' on its website. 'Hot Topics' is a series of articles on current, popular issues among doctors. These articles outline the GMC's position and the resources available to support doctors.

8.4 The GMC article stated the current legal position on prescribing off-label and tackled misperceptions. The article also reinforced the point that off-label medicines can, and are, being prescribed now, where there is robust evidence to support their efficacy and safety in the off-label indication. 'Hot Topics' are available on the GMC website for a limited period of time.

What pharmacovigilance takes place on off-label indications?

8.5 Off-label indications have not been approved through a regulatory procedure so there is currently no precedent for the application of normal medicine risk management tools. These include post-authorisation studies or the introduction of risk minimisation measures in product information for healthcare professionals or patients. However, MAHs (market authorisation holders) are required to collect and report any information on adverse reactions associated with either licensed or off-label use of the medicine. Furthermore, the 'Yellow Card' scheme run by MHRA, which is used to collect

reports of suspected side effects of medicines, could provide feedback at a UK level on any safety concerns with a licensed drug used in an off-label indication. More information about the 'Yellow Card' scheme here.

8.6 The 'Yellow Card' scheme is reliant on reporting by healthcare professionals and patients. Healthcare practitioners have been reluctant in the past to report adverse events associated with off-label use but are encouraged to do so. Signals from adverse events associated with off-label use are acted on by MHRA and manufacturers of the drug, even if the indication is not licensed.

8.7 Although MHRA does not recommend off-label use, it has published recommendations on a 'prescribing hierarchy' for licenced, 'off-label' and unlicensed medicines[10].

Outcomes for patients

8.8 Prescribers will give mindful consideration of the outcomes for, and impacts on, their patients - both positive and negative.

[10] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf

9. SHARED DECISION-MAKING

This chapter outlines support for prescribers and patients to make better treatment decisions together.

9.1 Shared Decision Making (SDM) is a collaborative process through which a clinician supports a patient to reach a decision about their treatment. The conversation brings together:

- the clinician's expertise: in areas such as, treatment options, evidence, risks and benefits; and
- what patients know best: their preferences, personal circumstances, goals, values and beliefs.

9.2 The decisions they reach with each other are informed by evidence on effective treatment, care and support. This leads to better decisions and outcomes for both the patient and clinician.

9.3 As well as the clinical reasons to undertake SDM, it is important from an ethical point of view to make sure that patients have unbiased and clear information on options, benefits and harms.

9.4 A recent landmark case, Montgomery v Lanarkshire Health Board (*Scotland, 2015),* has focused on the legal requirements to undertake Shared Decision Making. The importance of a patient's right to make their own decision has been advocated in legal cases before, but the Montgomery case confirms that the need for informed consent is firmly part of the law.

9.5 This ruling recognises the importance of patient self-determination and the ability of patients to understand the consequences of particular treatments. Clinicians now have a clear duty to take reasonable care to make sure that patients are aware of material risks. Shared Decision Making is a key way of ensuring this.

9.6 There is further information available on the NHS England website here

Patient Decision Aids (PDA)

9.7 A Patient Decision Aids (PDA) is a tool that presents evidence-based estimates of the benefits and risks of the available treatment options in sufficient detail that people can better judge their value. In contrast to health education materials, which simply provide broad background information, PDAs are tailored to a patient's health status and help them to make specific, personal choices about their treatment. Importantly, PDAs are intended to supplement or support the interaction between the person and their healthcare professional, rather than replace it.

9.8 NICE supports SDM through its guidance and tools, and leads a shared decision-making collaborative involving over 40 health and social care

organisations and patient groups. The collaborative produced a consensus statement and has agreed an action plan that includes the development and quality assurance of patient decision aids. This is available here. NICE has also developed a PDA on chemoprevention of familial breast cancer, in tandem with its updated guidance in this area which was published in March 2017.

Patients Involved in NICE (PIN)

9.9 NICE routinely discusses its guidance with Patients Involved in NICE (PIN), a coalition of over 80 patient organisations which enable patient groups to engage productively with NICE. PIN is independent from NICE and the pharmaceutical industry and meets with NICE on a quarterly basis to help shape and develop NICE's work.

9.10 NICE has also engaged with PIN to check their understanding of current prescribing arrangements and how this might be reinforced to address issues around repurposed medicines.

10. RECOMMENDATIONS

Licensing

10.1 MHRA licensing should be the preferred route for making repurposed, generic medicines available for use in the NHS.

Financial incentives for generic manufacturers

10.2 A financial incentive for generic medicines manufacturers to participate in medicines repurposing should be established, by extending the scope of HMRC Research & Development Tax Credits to include the repurposing of generic medicines.

10.3 A UK Catalyst Fund should be explored to establish the UK as a leader in medicines repurposing.

Testing the drug repurposing framework

10.4 One or more repurposed drugs should be selected and used, at the earliest opportunity, to test the framework outlined in this report. The outcome and any recommendations for changes to the framework or any of its elements should be shared with the Drug Repurposing Group by end of 2018.

10.5 The time it takes for a drug to progress through the framework should be monitored with a view to setting expectations for how quickly the system will respond to robust evidence in the future. The uptake should be included within the evaluation with a view to making recommendations on how to ensure clinical confidence in prescribing repurposed drugs.

Education of healthcare professionals

10.6 Once developed, healthcare professionals should be supported to understand the availability of resources that can support prescribing decisions for repurposed medicines. This includes education about the responsibilities in relation to the off-label prescribing of medicines, the need for shared decision making and obtaining informed consent and where to access high quality information, e.g. the BNF.

BNF

10.7 The BNF should continue to review its policy on inclusion of off-label uses of medicines in the Formulary. This should ensure that it routinely considers off-label uses where there is robust evidence that the benefits outweigh any risks.

MHRA support

10.8 MHRA should proactively communicate that clinical trial protocol advice, scientific advice sessions and the Innovation Office are available to medical research charities, academic research groups and other stakeholders.

10.9 Medical research charities, academic groups and other stakeholders should use MHRA scientific advice in order to ensure that evidence generated (through their clinical research programmes) is robust, and to determine the appropriate process by which a repurposed drug can be licensed.

Accelerated Access Collaborative

10.10 The Accelerated Access Collaborative should horizon scan to ensure that repurposed medicines are included in the Accelerated Access Pathway.

Regional Medicines Optimisation Committee

10.11 The newly formed RMOC should provide a route via which advice on the use of repurposed medicines from CCGs can be considered and utilised.

11. NEXT STEPS

11.1 To identify a list of repurposed drugs with practice-changing clinical research data, available now and over the next three years.

11.2 To evaluate three repurposed drugs for licensing or progress through the drug repurposing framework, with progress to be evaluated at the end of 2020.

11.3 To engage with HMRC and others on expanding the scope of R&D Tax Credits to include repurposing of generic medicines, or other incentive mechanisms.

11.4 To engage with the relevant agencies regarding the establishment of a UK Catalyst Fund for repurposed medicines.

11.5 To communicate the recommendations of the report through one or more workshops for medical research charities, researchers and others involved in medicines repurposing.

11.6 The Drug Repurposing Group to meet at the beginning of 2019 to evaluate progress made on next steps and agree any further actions.

12. ANNEXES

A - Membership of the Drug Repurposing Group

1. Association of Medical Research Charities
2. Department of Health
3. NHS England
4. The Medicines and Healthcare products Regulatory Agency
5. The National Institute for Health and Care Excellence
6. British National Formulary
7. Parkinson's UK
8. George Pantziarka TP53 Trust
9. Anticancer Fund
10. The Brain Tumour Charity
11. Prostate Cancer UK
12. Breast Cancer Now
13. Cancer Research UK
14. The Cure Parkinson's Trust
15. MS Society
16. Alzheimer's Research UK
17. Pharmacy Research UK
18. Institute of Cancer Research
19. Brain Tumour Research
20. Wellcome Trust
21. King's College Hospital
22. Gloucestershire Clinical Commissioning Group

23. Health Research Authority
24. Genesis Breast Cancer Prevention Centre
25. Royal Pharmaceutical Society
26. Royal College of Physicians
27. Royal College of Radiologists
28. British Generic Manufacturers Association
29. Association of the British Pharmaceutical Industry
30. General Medical Council
31. UK Therapeutic Cancer Prevention Network
32. Specialist Pharmacy Service
33. Nick Thomas-Symonds MP, Chair, All Party Parliamentary Group on Off Patent Drugs

B - **Legislation and Evidence from medical research charities**

Off-patent Drugs Bill

1. The Off-patent Drugs Bill was tabled in Parliament twice in two years. The first instance was in July 2014, when the sponsoring MP was Jonathan Evans, and the second was June 2015, when the MP was Nick Thomas-Symonds.

2. Both Bills required the Government to seek licences for off-patent drugs when there was evidence that they could be clinically effective for a new purpose and in instances when no pharmaceutical company had sought a licence. They also intended to require these drugs to be referred to NICE for a technology appraisal which, if positive, would give the NHS a legal obligation to fund them.

3. Both Bills received strong support from many MPs and medical research charities, with Breast Cancer Now being the main supporter. On second presentation a refined version of the Bill received the support of NHS Clinical Commissioners, the Royal College of Physicians, the Royal College of GPs, the Royal College of Radiologists (which includes oncology), and the British Medical Association.

4. Having talked to clinical experts including NICE, the National Clinical Director for Cancer and the Chief Pharmaceutical Officer, the Government was unable to support the Bill. There were two essential reasons for this:

   - It would have been a conflict of interest for the Secretary of State (SoS), as head of the UK licensing system, to become a regular applicant for medicines licences or for another body to do this on behalf of the SoS. Although on second presentation, the Bill was refined in order to try to address the conflict of interest issue. This was achieved by splitting the duties between DH and the Department of Business, Innovation and Skills. However, this was ineffective, as responsibility lay outside the Department of Business, Innovation and Skills therefore the Government felt that a conflict of interest remained.

   - By creating additional procedures for them in the Department of Health, the Government was concerned that the Bill would have the unintended consequence of creating further barriers for repurposed drugs, rather than freeing up access. It would have created a queue of drugs awaiting licensing applications followed by NICE Technology Appraisals (TA). They were concerned that clinicians would want to await the outcome of these, before using the drugs in the new indications. This would have created a real risk that the Bill would have led to more defensive prescribing behaviour, which would not have been in the interests of patients.

Access to Medical Treatments (Innovation) Act 2016

5. The Access to Medical Treatments (Innovation) Act 2016 received Royal Assent in 2016. It confers powers to enable more systematic sharing of information on innovative treatments. Amendments were introduced during the Bill's passage to ensure that medicines being used off-label and off-patent would be included within the definition of innovation.

Evidence from the charities

6. With repurposing becoming increasingly prominent, medical research charities invest a large amount of money in research looking at repurposed drugs. They want to see a "clear access pathway" for treatments so that the patient groups they represent can benefit. The medical research charities had received feedback from their members and clinicians, indicating that a number of issues were creating barriers to the flow of new research findings into practice and patient benefit.

Fear of prescribing off-label/unlicensed

7. Some clinicians, particularly GPs, felt unable to prescribe new off-label or unlicensed indications, even where the supporting evidence was robust. The lack of an entry in the BNF was a contributing factor for some clinicians. Other clinicians mentioned the lack of an agreed protocol, the fear of being sued and not having enough time to review research findings and/or undertake the additional administration and monitoring required when prescribing without a licence.

Prescribing for chemoprevention

8. Evidence of some healthcare professionals' (HCPs) reluctance to prescribe off-label was particularly strong in relation to the use of tamoxifen and raloxifene to reduce the risk of breast cancer in high risk populations (known as 'chemoprevention'). Further anecdotal evidence from leading clinicians in the field of chemoprevention illustrated how this problem is confounded in some areas by the addition of poor connections and/or trust between tertiary/secondary and primary care when prescribing is delegated to the GP.

9. Commissioned research from Cancer Research UK sought to understand GP attitudes towards the prescription and use of tamoxifen and aspirin to lower the risk of cancer, or to prevent cancer. Several factors influenced clinicians including:

- Clinicians' perceived lack of benefit from preventative therapy;
- Awareness of the NICE familial breast cancer guidelines - only 24% were aware;
- Clinicians feeling poorly informed about preventive therapy, and therefore discouraged from discussing with patients;

- GPs being unfamiliar with the concept of preventative therapy and unaware that they may be asked to prescribe it for high-risk women; and

- GPs being reluctant to begin therapy because the medicine was not licensed although GPs were willing to continue a prescription if the medicine had been prescribed in secondary or tertiary care.

10. The UK Therapeutic Cancer Prevention Network (UKTCPN), articulated that the barriers to routine availability of repurposed drugs that remain off-label or unlicensed were particularly high in the field of prevention, where:

    a) The prescriber is often a GP and not a specialist;

    b) The HCP has a duty to 'first do no harm' and is dealing with a person who is currently well; and

    c) The risk/ benefit decision can be challenging to explain, especially for a non-specialist.

11. In the case of chemoprevention, all of these factors are in play and there is a particularly difficult risk/benefit decision to be explained and made, given the side effect profile of these drugs.

12. Without a licence and a sponsoring company, the new indication was not advertised to health professionals, and therefore awareness of the treatment was low. Moreover, it is illegal to advertise a drug for an indication for which it is not licensed.

Understanding of terminology

13. Evidence showed that the understanding of HCPs of off-label and unlicensed indications is relatively low. At the Royal College of GPs annual conference in 2013, research findings were presented from a survey of 80 respondents (46 paediatricians, 29 GPs and five foundation year doctors). The survey sought to find out their interpretation of the phrase 'not licensed for use in children'. Results were as follows:

    - 61% thought it meant 'safety untested'

    - 58% thought 'not to be marketed' (correct answer)

    - 45% thought 'efficacy untested'

    - Eight trainee doctors thought supplying unlicensed drugs was illegal and seven thought it was illegal to prescribe. Only 58% of consultants and 46% of qualified GPs answered correctly.

Drug appraisal

14. Repurposed indications were rarely appraised by national commissioning bodies, such as NHS England, in the same way that indications were when they had a marketing authorisation. A statistically significant survey of UK breast cancer clinicians, conducted by the UK Breast Cancer Group in October 2016, showed that the majority of those trying to offer bisphosphonates for the prevention of secondary breast cancer were unable to do so, due to the lack of an agreed funding protocol. Medical research charities were concerned that even with a low cost off-label treatment, such as bisphosphonates, it was very difficult to make it routinely available without a nationally agreed and communicated commissioning policy.

15. Evidence showed that some HCPs were reluctant to offer the treatment without an agreed prescribing protocol and/or recognised clinical appraisal from a national body such as NICE.

16. Given this evidence, further work was needed to define and understand the subtler issues at play and a roundtable event, *'Translating evidence into clinical practice',* was convened to examine these. Please refer to *Annex C* for details.

C - **Translating evidence into clinical practice**

1. The roundtable event, 'Translating Evidence in to Clinical Practice', took place in February 2015 and explored, in depth, the issues around the culture of unlicensed and off-label prescribing in general. NICE, Breast Cancer Now, The Cure Parkinson's Trust, Cancer Research UK, NHS clinicians, MHRA, the GMC and Mr Jonathan Evans MP (the Hon. Member who tabled the original Off-patent Drugs Bill) were all in attendance.

2. The meeting examined what action, short of legislation**,** could be taken to improve the flow of research evidence into clinical practice and better support the use of off-label medicines in areas where the evidence suggests that they can deliver patient benefit. The discussion conveyed the complexity of the area with a number of factors at play.

Drug repurposing pathway

3. There was no clear and systematic pathway for researchers to follow to transfer their evidence into clinical care. Systems relied on individual clinicians to champion new research, leading to duplication of effort, as well as slow and patchy uptake. Researchers and charities needed better knowledge and an agreed pathway with Government agencies of how to get research findings into the system and through to licensing.

Prescriber knowledge

4. Prescribers needed better and more accessible information about licensing status and its implications. Some prescribers were confused over responsibility for prescribing between secondary and primary care, whilst others lacked the confidence and/or the time to prescribe off-label, even when evidence was available and accessible.

Patient attitudes

5. Patient attitudes were an important factor in making prescribing decisions and some prescribers lacked the specialist knowledge to have the detailed risk/benefit discussions necessary when prescribing outside the terms of the licence.

Surveillance

6. Surveillance systems (such as those hosted by NICE and NIHR) could be tailored to better identify promising research which is taking place on repurposed drugs. By horizon scanning this would leave more time to support translation of the repurposed drug into clinical practice.

Appraisal

7. There was no established system for a repurposed drug to be clinically appraised or approved for routine commissioning by national bodies, yet this guidance was needed in order to better support access for patients.

The British National Formulary (BNF)

8. Most licensed treatments were automatically included in the BNF, whereas off-label treatments were only published if they were already being used commonly in clinical practice. This created a 'chicken and egg' situation because an off-label treatment was unlikely to make it into common clinical practice if it was not in the BNF.

Variations in prescribing decisions

9. Discussions with NICE revealed evidence of some drugs that had both a licence and a positive technology appraisal (TA) yet still had problems being adopted into routine clinical practice. Such cases could occur as a result of variation in prescribing decisions which was inevitable, and also appropriate, given some patient choices for their treatment.

10. Research from NICE into prescriber behaviour showed that prescribing decision-making follows the same well understood patterns of behaviour as other human decision making, where prescribers tend to rely on existing behaviour patterns that are predisposed, rather than on the creation of new patterns and behaviours. Critical factors in the decision-making process include:

- Interaction with colleagues and peers;
- Professional training;
- Personal experiences; and
- Cognitive biases, i.e. going for an obvious diagnosis; with thinking being shaped by prior expectation.

11. Additionally, the path from research into clinical practice was not a straightforward one. It involved a number of translations (i.e. from research to national guidance; from national guidance to local implementation; from local implementation to individual decision-making. Each translation required these new patterns of behaviour and decision-making to be effective.

12. There was a genuine commitment to improve matters and investigate what non-legislative steps could be taken to support appropriate medicines use and benefit NHS patients. Participants identified a range of potential actions that would help and some of these were pursued by NICE and the GMC.

D - **Case Studies: Bisphosphonates and Docetaxel**

1. This annex presents two examples of repurposed off-patent medicines in relation to the drug repurposing framework. These are bisphosphonates for preventing secondary breast cancer and docetaxel (in addition to standard hormone therapy) in metastatic prostate cancer. NHS England developed and agreed a policy statement for routine commissioning of docetaxel in this indication through Specialised Services.

Bisphosphonates for preventing secondary breast cancer

2. Bisphosphonates are a group of drugs that are licensed to treat osteoporosis and to reduce the damage to the bones caused by cancer that has spread there. The bones are a common place to which breast cancer can spread.

3. Because of bisphosphonates' impact on bones, it was anticipated that they could modify the process of cancer spreading to the bones. Many randomised controlled trials have been performed to investigate this. A large collaborative meta-analysis of 26 randomised controlled trials involving nearly 19,000 women was undertaken.

4. The results were published in the Lancet in 2015. The study showed that giving a bisphosphonate to post-menopausal women with primary breast cancer could reduce the risk of breast cancer spreading to the bone within 10 years by nearly a third; reduce the risk of breast cancer spreading to any site, including the bone, within 10 years by around a fifth; and reduce the risk of death from breast cancer within 10 years by a sixth. Both the UK Breast Cancer Group and NHS England Clinical Expert Group have recommended prescribing bisphosphonates for post-menopausal women with primary breast cancer.

5. Bisphosphonates are off-patent and have been available generically for many years. At the time, no pharmaceutical company was actively pursuing a licence for bisphosphonates for preventing breast cancer spreading to the bone in post-menopausal women with primary breast cancer.

6. DH and NHS England have said that CCGs have primary responsibility for commissioning bisphosphonates in this new indication. However, a Freedom of Information request to CCGs suggests that only 20% are currently routinely commissioning bisphosphonates for this indication, with a further 6% that have agreed to commission them implementing their decision.

Adoption of docetaxel chemotherapy earlier in the treatment pathway for men with advanced prostate cancer

7. In 2015, the STAMPEDE[11] clinical trial reported that men with metastatic prostate cancer who were taking docetaxel chemotherapy at the same time as hormone therapy lived for an average of 15 months longer than those taking hormone therapy (ADT) alone. At the time of the trial, docetaxel chemotherapy was routinely available for men with advanced prostate cancer. However, it was only prescribed after men had become resistant to ADT, as per the licence.

8. These trial results indicated that docetaxel could be considered to be made available to patients with advanced prostate cancer earlier in the treatment pathway, alongside ADT. However, as docetaxel is an off-patent treatment, no manufacturer was incentivised to engage with either NICE or NHS England to translate these findings to clinical practice. Therefore, Prostate Cancer UK worked with NHS England to establish a fast-track route to commissioning earlier docetaxel, which would enable men with advanced prostate cancer to have access to it at the first opportunity.

9. As the use of docetaxel in this new indication would be outside its licensed indication, it was necessary for NHS England to produce a Clinical Commissioning Policy Statement. To set this in motion, the clinical trial team shared results with NHS England prior to publication. These results provided an indication of the scale of clinical benefit. As soon as the trial results were published, NHS England commissioned NICE to undertake a Rapid Evidence Review (RER), which assessed the research findings. Alongside this a Financial Impact Assessment (FIA) was produced to determine whether this could be developed as an in-budget commissioning policy.

10. In this case, the RER and FIA were finalised within five days of publication of the trial data. Using this information, a draft Commissioning Policy Statement was compiled by NHS England's Chemotherapy Clinical Reference Group. This was then considered at an extraordinary meeting of the Programme of Care Board for review, and then by the Clinical Priorities Advisory Group (CPAG) to make a formal recommendation on the policy statement. CPAG's recommendation went on to NHS England's Specialised Commissioning Oversight Group (SCOG) for an assessment of available resources and commissioning implications. SCOG gave the final decision on the Policy Statement and approval for routine commissioning was granted on 20 January 2016.

11. This fast-track approach delivered change to the treatment pathway in a matter of weeks – from publication of trial findings to approval of an in-budget commissioning policy statement for an off-patent treatment. Critical to success was: *early engagement, access to the NICE medicines team, and flexibility within NHS England to accommodate consideration of the propositions*. It also relied on continuous support from Prostate Cancer UK for momentum.

[11] James ND, Sydes MR, Clarke NW et al. (2015) Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. The Lancet http://dx.doi.org/10.1016/S0140-6736(15)01037-5

E - Glossary

ABPI – Association of the British Pharmaceutical Industry

BGMA – British Generic Manufacturers Association

BNF – British National Formulary

CPAG – Clinical Priorities Advisory Group

DH – Department of Health

EMA – European Medicines Agency

FIA – Financial Impact Assessment

Generic drugs – is commonly used to mean drugs where the patent has expired, and they are being made and marketed by a number of different pharmaceutical companies, e.g. Simvastatin.

GMC – General Medical Council

HMRC – HM Revenue & Customs

Licence – a medicines marketing authorisation

MA – Marketing Authorisation also commonly called a licence

MAH – Marketing Authorisation Holder

MHRA – Medicines and Healthcare products Regulatory Agency

NHS CC – NHS Clinical Commissioners (the representative body for local Clinical Commissioning Groups)

NICE – National Institute for Health & Care Excellence

NIHR – National Institute for Health Research

Off-label – a licensed drug which is being used outside its licensed indications, e.g. for a patient who is not among the patient group named on the licence or to treat a medical condition which is not included in the licence or in a dosage which is different from that specified on the licence.

Off-patent – the patent protection has expired, and other companies can apply for a licence for it and produce their own version of the medicine, when periods of data and marketing exclusivity in medicines legislation have also expired. Patent and exclusivity periods have different legal frameworks and run in parallel, often expiring around the same time.

Pharmacovigilance (PV) is defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

RMOCs – Regional Medicines Optimisation Committees

SCOG – Specialised Commissioning Oversight Group

SME – Small and Medium Size Enterprises

Unlicensed – a drug for which there is no marketing authorisation (licence)