Opportunities to Repurpose Medicines in the NHS in England

Recommendations of the Medicines Repurposing Programme Board 2019/20 and Proposed Forward Work Programme 2020/21 - 2022/23

NICE National Institute for Health and Care Excellence

NIHR | National Institute for Health Research

Department of Health & Social Care

MHRA Regulating Medicines and Medical Devices

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Executive Summary

The Repurposing (originally 'Off-Label') Medicines Programme was established to identify and pursue opportunities to strengthen the evidence base, licencing, supply and cost effectiveness of un-licenced or off label medicines in current (or likely future) common use in the NHS.

Organisations represented on the programme board want to ensure that, in future, barriers are minimised for any 'repurposable' medicines that have a significant potential value in terms of improving patient care and associated outcomes and are likely to be able fulfil the requirements for routine funding in the NHS in the future.

The experience of member organisations in collaboratively managing the rapid consideration and adoption of repurposed medicines as treatments for COVID-19 has provided the opportunity to test, refine and streamline our approach, as well as identifying further promising repurposing opportunities.

The programme has prioritised the following recommendations and an update on resulting actions is provided below:

Issue	Recommendations	Actions Completed / Planned
Opportunity Identification	Building on early work with charities and lead clinicians, horizon scanning should now be formalised, through the NIHR Information Observatory, to provide systematic intelligence on future repurposing opportunities of benefit to the NHS.	Initial pilot topics have been identified and licensing options are now being pursued in partnership with charities and the BGMA. Repurposed medicines have been added to the development pipeline for the NIHR Information Observatory, for implementation in 2021/22. A mechanism will be identified to enable candidate repurposing opportunities to also be put forward by stakeholders, for consideration, dovetailing with the Accelerated Access Collaborative (AAC).
Progressing Repurposing Opportunities	A 'route map' should be articulated, and tested, to help identify the actions that will best expedite the repurposing of identified and prioritised candidate medicines.	A draft route map has been developed and is therefore now available for further testing and refinement with initial pilot topics, taking into account learning from the rapid adoption of medicines repurposed to treat COVID-19. This process aims to identify the best option to underpin future equitable access to the repurposed medicine in the NHS.
	A programme team should now be established, drawing in expertise from MHRA, NICE and NIHR, as well as organisations with direct experience of achieving market authorisations, to progress the pilot topics identified, formalise the identification of future topics and complete the further actions agreed.	A package of multi-agency expert support, underpinned by an incentives programme, will be established as part of a new national repurposing medicines programme, with a target of initially supporting 2-3 new indications per year to the point of licencing. This will increase to up to 6 indications per year by year three.

		Funding has been secured to enable a small programme team to be established in autumn 2020.
	For identified priority candidate medicines, a discussion should be held with the existing licence holder, where a market authorisation for a branded product is already in place, to identify the potential for a future licence variation and supporting clinical commissioning policy or other national guidance.	A manufacturer stakeholder surgery mechanism, linked to the clinical commissioning policy pipeline, is already available within NHS England's direct commissioning function as a mechanism to deliver this recommendation
	A package of support should be made available, with financial incentives where appropriate, to encourage generic manufacturers (and other potential licence holders) to seek variations to existing market authorisations to support repurposing. This may include the establishment of a 'catalyst' type fund, against which potential licence holders can apply. A parallel incentive mechanism may be appropriate to support existing licence holders (for example repurposing a medicine for a small patient cohort).	Discussions are being held with the Office of Life Sciences (OLS) and the Department of Health and Social Care (DHSC) in relation to the potential to establish a repurposed medicines 'catalyst' fund.
Evidence Generation	Where evidence gaps are identified for medicines prioritised for repurposing, fast-track evidence generation should be established using either existing or bespoke routes, working with partner organisations including MHRA, NICE and NIHR.	NHS England will work with the MHRA, NICE and NIHR, under established partnership arrangements, to identify the most appropriate route to fast-track evidence synthesis and generation for prioritised topics.
Ensuring Best Price through Competition	The introduction of a new repurposed indication for an off patent generic medicine should not interfere with the competition between manufacturers that effectively keeps prices down. Therefore, it will be preferable if any incentives for generic manufacturers to repurpose a medicine are delivered in a way that does not impact existing pricing and reimbursement systems, which promote effective competition.	NHS England is working with the OLS to consider how an incentive might be made available to the manufacturer who takes the lead in adding the repurposed indication to their existing Marketing Authorisation (MA). Competitors would then add the indication to their MAs (using an existing simpler and quicker regulatory process) so maintaining the level playing field.
Supporting Adoption	NHS England should build on its expertise in national clinical commissioning policy determination to offer CCGs completed template policy proposals for prioritised off label medicines, for review and discretionary adoption.	NHS England has published 35 policies supporting equitable access to off-label medicines in specialised care as part of its wider policy programme (see Appendix 2). NHS England has also led the development and adoption of the first UK wide policy for Remdesivir in the treatment of COVID-19. Discussions will be held with NHS Clinical Commissioners to pilot the template policy approach for CCG commissioned medicines.
	A business as usual process should be established so that NICE guidance and national commissioning policy decisions on the routine use of off label medicines are incorporated into the British National Formulary (BNF), guiding day to day prescribing decisions, without delay.	BNF Publications has agreed to provide a link to national policy decisions for both on and off label medicine use in its publications.
	NICE should consider ways to support guidance development for newly licenced (repurposed) medicines where there is a smaller market authorisation holder (e.g. generic manufacturers) who may have a more limited supporting governance and regulatory infrastructure than larger pharmaceutical companies.	NICE is considering whether its methodology should and could be reviewed to provide clearer guidance for repurposed medicines when considered in a guideline.

	NICE should consider whether it is possible to pilot an adapted approach for off-label medicines so that high quality guidelines can be produced to better inform commissioning decisions.	

Background

1. In December 2017 the Association of Medical Research Charities (AMRC) published a report[1] which focused on the opportunities for repurposing medications through facilitating better research into, or licencing of, medicines commonly prescribed off-label.
2. The report acknowledged that, despite limited routine data, there are likely to be high levels of off-label prescribing in England.
3. The report made recommendations for consideration by the Department of Health and Social Care (DHSC) and some arms-length bodies, including NHS England and has generated a great deal of interest, including amongst the research community and patient groups, in how progress can now be made in addressing off-label prescribing.
4. NHS England's Board made a commitment to identify and pursue key opportunities to improve off label prescribing at its meeting in December 2018, and the Off-label Medicines Programme Board was subsequently convened in 2019. The Board includes representation from (see Appendix 3):
    - NHS England and Improvement
    - The Department of Health and Social Care (DHSC)
    - The Medicines and Healthcare products Regulatory Authority (MRHA)
    - The National Institute for Health and Care Excellence (NICE)
    - The National Institute for Health Research (NIHR)

Definitions

5. **Repurposing**: Drug repurposing (also called drug repositioning, reprofiling or re-tasking) is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication.[2] It typically involves taking an existing medicine that has a marketing authorisation (MA) or licence for human use in one condition and using this medicine to treat another condition.
6. **On-label vs Off-label**: A medicine will usually be prescribed to an individual in line with the scope of the medicine's market authorisation (or product licence). This will include:
    - use of the medicine only for specified therapeutic indications in line with the evidence base submitted to the regulators at the time of licensing
    - appropriate administration within dosing recommendations (as above)
    - use of a properly labelled product
    - provision of standardised patient information
    - taking into account listed contraindications and precautions

    Off label use is where a medicine is administered outside the scope of the market authorisation, for example by using a different dose, administering the drug in a different way or using a medicine licenced only for adults for a child. Clinicians are asked to consider using medicines off label only where there is not a suitable available licenced product and where

[1] https://www.amrc.org.uk/blog/facilitating-adoption-of-off-patent-repurposed-medicines-into-nhs-clinical-practice

[2] *MRC Centre for Drug Safety Science, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK*

they are sufficiently satisfied that there is evidence of the medicine's safety. More details can be found here: https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities.

7. **Patent and Off-Patent**: When a developer creates or identifies a new chemical or drug that they believe may have therapeutic value, they can apply for a patent, granting them exclusive rights to market the product for up to 20 years. After 20 years, or sooner if renewal requirements are not met, the drug becomes 'off-patent', and generic versions can be marketed by other companies, subject to any market authorisation restrictions (data and market exclusivity period protections). The patent period can be extended for a further period of 5 years (or 5 years and 6 months for some paediatric products) where a Supplementary Protection Certificate (SPC) has been secured and a market authorisation is in place.

   During the patent protection period, the developer may undertake years of development and phased trials ahead of achieving a market authorisation, and potential commercial gain, hence the additional protections of data exclusivity and market protection offered post market authorisation.

8. **Data Exclusivity and Market Protection**: Market authorisation (licence) holders are typically granted an 8-year period of data exclusivity and a concurrent 10-year period of market protection.

   During the data exclusivity period, a(nother) applicant cannot use or rely on the data to submit an application, obtain market authorisation or place the product on the market.

   During the market protection period, a generic, hybrid or biosimilar cannot be placed on the market, even if a market authorisation has been achieved.

9. **Orphan Status**: Orphan status recognises the commercial challenges specific to medicines developed for small numbers of patients. EMA orphan status designation offers the sponsor the potential for protocol assistance, dedicated scientific advice, fee reduction and 10 year (+2 for paediatric medicines) market exclusivity.

   To apply, a medicine must meet a number of criteria:

   - it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
   - the prevalence of the condition in the EU must not be more than 5 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;
   - 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.

   During the period of market exclusivity for an orphan product, a marketing authorisation may be granted, for the same therapeutic. indication, to a similar medicinal product if:

   - the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or;
   - the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or;
   - the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

Current Practice

10. Off-label prescribing is part of normal clinical practice. When prescribing, clinicians must follow what is known as the 'prescribing hierarchy': the first choice should be a licensed

medicine used within its licensed indication; if that is not clinically suitable for the patient, clinicians can use a licenced medicine outside its licenced indication (off-label prescribing); and then finally if that is not clinically suitable for their patient then they can use an un-licenced medicine.

11. Clinicians can therefore make a decision to prescribe off-label on a patient-by-patient basis, if they are satisfied that an alternative licenced medicine would not meet the patient's needs as well as the off-label indication, and that there is a sufficient safety and efficacy evidence and/or experience.
12. Off label prescribing is therefore effectively at the discretion (and professional liability) of the individual clinician, leading to significant variation in practice. Concerns include the lack of an agreed protocol, the fear of litigation and not having the resource to review research findings and/or undertake the additional administration and monitoring required when prescribing outside of a licence.
13. Off-label medicines have not undergone health technology appraisal, licensing, or equivalent evaluation for an alternative indication, dose, formulation, mode of delivery, or population.
14. However, off-label prescribing can be beneficial to patients and the NHS; many new and valuable uses of medicines have been discovered through off-label prescribing and are now in widespread use in the NHS. For example: aspirin is now used primarily for cardiac problems rather than as pain relief, and tricyclic antidepressants were found to be one of most effective treatments for neuropathic pain relief.[3]
15. Enabling access to an un-licenced, or off-label, drug may also provide faster access to an effective treatment either ahead of planned licencing or where the cost of developing and licencing a new medicine may not be financially viable for industry, e.g. in rare diseases where patient numbers are small.
16. In some cases, a drug company may have sufficient evidence that a drug is clinically effective in a new indication or population, but there may be no commercial incentive to licence it – for example where the drug is already low cost or generic. In other instances, a company may decide it is too challenging to collect sufficient evidence to licence the drug, particularly where the patient population for the new indication is very small (e.g. for gene therapies) or is challenging for ethical or regulatory reasons (i.e. in children).

Benefits of Securing a Licence for an Off-label Medicine

17. Licensing a product brings a number of potential benefits. It reduces the individual burden on clinicians by reassuring both them and their patients that the use of a medicine in a given indication is evidence based, it avoids the need for special preparation, labelling and bespoke patient information, and provides assurance that the drug is subject to ongoing pharmacovigilance.
18. A licenced product may respond to one or more previously unmet needs, offer patients more consistent access to a safer or more effective treatment, offer a more acceptable route of administration (such as a tablet replacing a current intravenous product) and / or offer a more cost-effective treatment option.
19. It also importantly facilitates more equitable access to medicines for patients (as a licence is a regulatory 'stamp of approval'). A licence also facilitates the development and agreement of national or other guidance and policy (for example NICE technology appraisals or NHS England clinical commissioning policy). It also supports consistency of

[3] Saarto, T. The Cochrane Database of Systemic Reviews, July 20, 2005. News release, Health Behavior News Service.

supply and cost efficiencies since manufacturers can be more confident of routine consideration of the product in relevant care pathways and resultant demand.

The Responsibilities of a Licence Holder

20. Post authorisation, market authorisation ('licence') holders have a number of ongoing responsibilities including pharmacovigilance, updating labelling and patient information, reporting medication errors, maintaining and acting upon a risk management plan, undertaking post-authorisation safety studies, submission of product data to the EMA or MHRA, and applying for any applicable market authorisation changes.
21. After authorisation, a medicine will typically be used for a larger number of patients, for an extended duration and in combination with other medicines than may not have been covered by initial clinical trials. The licence holder is therefore required to have a qualified person responsible for pharmacovigilance and will operate a tailored pharmacovigilance system covering the detection, assessment, understanding and prevention of any medicine related problem once the medicine is in wider routine clinical use.

The MHRA Procedure for Varying the Licence for New Indication or New Formulation

22. The current licensing system for medicines ensures that patients receive medicines that have been scientifically assessed to meet published European standards of quality, safety, and efficacy. These standards are applied and enforced in the UK by the Medicines and Healthcare Products Regulatory Agency (MHRA).
23. Applicants are able to apply for a single country/state market authorisation, or for multi-country or EU wide market authorisations by first applying through a lead country (the 'leading authority') and then requesting mutual agreement or other 'piggybacking' arrangements. Under the EU exit withdrawal agreement, the UK will be unable to act as a 'leading authority' for applications during the transition period. However, the MHRA may now be in a stronger position to develop alternative, innovative licensing and access pathways.
24. The MHRA has a clear, and relatively simple, process for a variation application (which takes about 6 months) for licensing medicines for repurposed uses. Clinical trials funded by NIHR or Medical Research Charities (MRCs) could be sufficient to support licensing. In some circumstances additional trial data will be needed (to be determined in a scientific advice meeting (SAM) with the MHRA).
25. Typical costs (assuming no additional evidence or safety data generation required) have been estimated as follows:

Activity	**Agency responsible for activity**	**Costs**
Preparation for MHRA scientific advice meeting	MA holder	c£20k
MHRA scientific advice meeting	MHRA	£3.6k
MHRA fees	MHRA	£8-25k
Regulatory dossier preparation and answering MHRA queries	MA holder	£35k
Product specific pharmacovigilance and Risk Management Plan (RMP)	MA holder	Average £50k (but up to £100k)
Company updating product information (in pack labels & leaflets) with the new indication	MA holder	£30k
TOTAL		**c£163k**

Within the Market Protection Period

26. During the market protection period, market authorisation holders (MAHs) can apply to vary their authorisation to include additional uses (indications), dosing or administration. The MAH can submit a variation for a new indication at any time but is only entitled to an extension of market protection if the variation for is a significant clinical benefit and is submitted within the first 8 years. By exception, and only with the express permission of the MAH, another organisation could also apply for a new market authorisation for the product during its market protection period.

Once the Market Protection Period Has Expired

27. Once the market protection period has expired, a generic or biosimilar medicine already approved by the MHRA can be used as the basis for the introduction of repurposed medicine, through the licensing route, by means of a type 2 variation application. This procedure assesses the efficacy and safety of the new indication, determining the benefit and the risk balance.

Licence Holder Options

28. 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.
29. It is feasible for other organisations including NHS organisations and medical research charities to become a licence holder; however, they would need to satisfy themselves that they could undertake the full role of a licence holder with all the obligations and financial costs that that entails. It is also worth noting that the incremental costs for an existing manufacturer would be significantly lower than for the NHS or charity who would have to establish new processes / teams. Alternative licence applicants may need to partner with a third party (potentially a consultancy, or drug company) who would be sub-contracted to assist with these responsibilities but even then, the process would take longer as there would be a need to apply for a full market authorisation (MA) whereas a company with an existing MA would only need to apply for a clinical variation to the existing MA; a significantly shorter and less expensive process.

The Holder of the Current Market Authorisation Applies for a Variation

30. Although market protection is usually for a period of 10 years, this period may be extended for a further year (to a total of 11 years) if the market authorisation holder obtains a variation for one or more new therapeutic indications that represent significant clinical benefit over existing treatments during the first 8 years.
31. A variation to the market authorisation to incorporate a new use identified (and evidenced) quite late within the market protection period may therefore offer limited commercial gain for the original market authorisation holder (MAH).

A Generic Manufacturer

32. Generic manufacturers are well positioned to apply for a variation where they already have a market authorisation for an existing indication as they have the necessary infrastructure and expertise to navigate the system and satisfy its requirements. However currently there is no way of them recovering their costs, therefore a new incentive is required.

The BGMA (supporting their members rather than as licence holders)

33. The British Generic Manufacturer's Association (BGMA) was a key stakeholder in the original AMRC report and has been working in partnership to identify and progress repurposing opportunities identified by AMRC member charities. Examples include bisphosphonates to prevent breast cancer recurrence and propranolol for in the treatment of angiosarcoma.

The NHS

34. NHS bodies may be well placed to seek and maintain market authorisations, although only a few NHS organisations currently choose to undertake pharmaceutical production (see case study below).

35. NHS England is currently exploring whether it could operate in this space. Given the responsibilities and liabilities of marketing authorisation holders, membership of the NHS Clinical Negligence Scheme for Trusts (CNST) is desirable and it is understood that membership of the scheme is open to the NHS Commissioning Board (NHS England). Depending on the options that the programme team wishes to pursue for individual candidate medicines, further formal legal advice to cover relevant scenarios will be sought.

Case Study:

Torbay Pharmaceuticals

Torbay Pharmaceuticals is the largest NHS-owned pharmaceutical contract manufacturer and licence holder, and forms part of Torbay and South Devon NHS Foundation Trust. Its portfolio includes licenced and un-licenced sterilised injectables, electrolyte ingredient solutions for total parenteral nutrition and a range of supporting products and services.

Uniquely for the NHS in England, it has sought and achieved 21 marketing authorisations (21 presentations across 6 medicines), as well as manufacturing medicines under contract for both NHS and commercial customers.

Currently licenced products include:

CODEINE PHOSPHATE 60mg in 1mL Solution for Injection	Ampoule	10 x 1mL
ISOSORBIDE DINITRATE 0.05% w/v Solution for Injection or Infusion	Vial	10 x 50mL
ISOSORBIDE DINITRATE 0.1% w/v Concentrate for Solution for Injection or Infusion	Ampoule	10 x 10mL
ISOSORBIDE DINITRATE 0.1% w/v Concentrate for Solution for Injection or Infusion	Vial	10 x 50mL
MAGNESIUM SULFATE 50% w/v Solution for Injection or Infusion	Ampoule	10 x 2mL
MAGNESIUM SULFATE 50% w/v Solution for Injection or Infusion	Ampoule	10 x 5mL
MAGNESIUM SULFATE 50% w/v Solution for Injection or Infusion	Ampoule	10 x 10mL
MAGNESIUM SULFATE 50% w/v Solution for Injection or Infusion	Vial	10 x 20mL
MAGNESIUM SULFATE 50% w/v Solution for Injection or Infusion	Vial	10 x 50mL
MAGNESIUM SULFATE 50% w/v Solution for Injection or Infusion	Vial	10 x 100mL
METARAMINOL 0.5mg/mL Solution for Injection	Ampoule	10 x 5mL
METARAMINOL 0.5mg/mL Solution for Injection	Ampoule	10 x 10mL
METARAMINOL 10mg/mL Solution for Injection or Infusion	Ampoule	10 x 1mL
MORPHINE SULFATE 1mg in 1mL Solution for Injection	Ampoule	10 x 1mL
MORPHINE SULFATE 1mg in 1mL Solution for Injection	Ampoule	10 x 5mL
MORPHINE SULFATE 1mg in 1mL Solution for Injection	Ampoule	10 x 10mL
MORPHINE SULFATE 1mg in 1mL Solution for Injection	Vial	10 x 50mL
MORPHINE SULFATE 2mg in 1mL Solution for Injection	Vial	10 x 50mL
SODIUM CHLORIDE 30% w/v Concentrate for Solution for Infusion	Ampoule	10 x 10mL
SODIUM CHLORIDE 30% w/v Concentrate for Solution for Infusion	Vial	10 x 50mL
SODIUM CHLORIDE 30% w/v Concentrate for Solution for Infusion	Vial	10 x 100mL

36. Breast Cancer Now – Bisphosphonates to Prevent Breast Cancer Recurrence.

    Bisphosphonates are a group of drugs which have been used for many years to strengthen bones and reduce the risks of osteoporosis. Breast Cancer Now played a key role in highlighting the findings of research that showed that biphosphates could also reduce the risk of breast cancer spreading to the bone, in post-menopausal women (an un-licensed use of this medicine). They have campaigned to progress options to support its routine use, including the publication of updated NICE guidelines on early and locally advanced breast cancer. The available data were derived from large randomised controlled trials of bisphosphonates in early invasive breast cancer, designed to test the hypothesis that bisphosphonates prevent bone metastases, and thereby reduce the risk of recurrence and increase overall survival. MHRA has stated that the evidence to support a licenced indication in the post-menopausal adjuvant breast cancer setting appears promising for zoledronic acid and clodronate.

Incentives

Extension to the Current One-year Exclusivity Period (existing licence holders)

37. Although market protection is usually for a period of 10 years, this period may be extended for a further year (to a total of 11 years) if the market authorisation holder obtains an authorisation for one or more new therapeutic indications during the first 8 years.
38. There may be options to establish a further extended market protection period (or extended timescale to apply for market variations) to incentivise existing market authorisation holders to apply for a variation to include a current off label use.
39. Ideally, to maximise leverage with pharmaceutical companies, this would be undertaken in collaboration with European colleagues who are equally looking at minimising current barriers to repurposing, or if necessary, within the UK only, under the freedoms offered following EU withdrawal.

Incentives for Generic Manufacturers

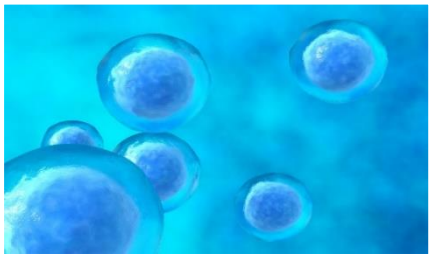
40. Generic companies have expressed interest in taking medicines through repurposing but currently there is no way of them recovering their costs therefore an incentive is required, designed in a way to prevent prices being increased. This currently appears to be a significant rate limiting step in progressing repurposing.
41. It is important that the introduction of a new repurposed indication for an off patent generic medicine does not interfere with the competition between manufacturers that keeps prices down. Therefore, it will be preferable if the incentive for manufacturers is delivered in a way that does not impact existing pricing and reimbursement systems, which promote effective competition. The incentive would be made available to the manufacturer who – identified through a competitive process - takes the lead in adding the repurposed indication to their Marketing Authorisation (MA). The other producers in the market would then be able to add the indication to their MAs (using an existing simpler and quicker regulatory process) so maintaining the level playing field.
42. NHS England is currently in discussion with the Office of Life Sciences to discuss a ‘catalyst’ type fund that might be established to support the licensing process in prioritised areas where current market and or regulatory requirements are acting as a bar to applications. NHS England has estimated that a budget of around £10.5m would be required to support 2-3 licence applications per year for three years, including generating additional evidence on safety and efficacy where required.
43. It will be important that any fund does not conflict with the State Aid provisions which aim to ensure that publicly (i.e. taxpayer) funded discretionary funded assistance to charities, public

authorities and other non-profit making companies involved in commercial activities does not adversely distort competition of affect trade between member states of the European Union.

Closing the Evidence Gap

44. Additional clinical evidence may be required to support market authorisation (or variations), the development of NICE guidelines or guidance, and clinical commissioning policy (routine NHS funding) decisions. There is therefore potential to better harmonise and articulate these, often overlapping, policy and regulatory requirements, particularly at the early stages of trial design and development.
45. NHS England has established a national evaluative commissioning programme in support of its commissioning role for specialised services. Programme deliverables include signalling evidence gaps identified either in clinical practice or in forming national clinical commissioning policy to research funding organisations, streamlining the way in which researchers gain access to NHS funding for the additional ('excess') treatment costs associated with approved studies and working in partnership with NICE and NIHR where a key study would not otherwise succeed through existing routes (for example for rare disease or other smaller treatment cohorts).

Case Study:



The Mesenchymal Stem Cell Study for Children with Epidermolysis Bullosa (MissionEB) was the first pilot topic taken through NHS England's National Research Collaboration Programme with NIHR.

Epidermolysis bullosa (EB) is an inherited disease where blistering follows minor injury because of a missing protein in the skin and other organs. Recessive Dystrophic EB (RDEB) is one of the most severe types of EB and may lead to disability and sometimes a reduced life expectancy. Blisters heal with scarring, and this process can lead to contraction of the joints, fusion of the fingers and toes, contraction of the mouth membranes and narrowing of the oesophagus, as well as recurring wounds, scarring, pain and itching. There is therefore a very significant quality of life impact for both the individual and their family, with a frequent need for dressing changes and restrictions on normal day to day activities. There is currently no curative treatment for RDEB and management is supportive.

Clinicians and affected families approached NHS England to share their positive early experience of using of stem cells, administered intravenously, in ten children with RDEB. This suggested that the therapy may reduce pain and itching, for between 3 and 6 months. Whilst there was a wish to seek a routine NHS commissioning position, it was acknowledged that more robust evidence of safety, clinical and cost effectiveness would be needed before a funding decision could be made for the circa 100 patients currently affected by this form of EB.

Working with families, lead clinicians, NIHR and other expert advisors an appropriate methodology was developed collaboratively, recognising both the need for robust research as well as the challenges of undertaking research with a very small, and largely paediatric, cohort of patients. The resulting, and now approved study proposal, called 'MissionEB', is a prospective, randomised, placebo controlled, double blinded, cross-over trial with an initial first phase to test the safety and dosing requirements for umbilical cord derived stem cells, which would be likely to be used in a future routine commissioning scenario. It has a planned sample size of 37, reflecting the feasibility of recruiting from the small population with this rare disease and will measure disease severity as measured by the iscorEB tool at 3 months and 12 months as the primary outcome. In addition, photographs will be taken and independently assessed, together with blood tests to check for inflammatory markers and impact on kidney and liver function.

The study will operate across two sites, Great Ormond Street Hospital for Children and Birmingham Children's Hospital, which together provide the commissioned paediatric highly specialised service for this condition.

46. Properly constructed research will always be seen as the 'ideal' in terms of supporting policy and regulatory requirements but where a formal trial is not deemed possible or likely, NHS England has an established partnership with NICE to develop alternative evaluative studies which generate real world data in a front-line NHS setting. 8 studies have been completed to date, the results of which have already been used to support decision making on the routine commissioning (funding) of a number of specialised treatments in the NHS. It is possible that this route could be adapted to generate the additional evidence required for market variations for generic medicines in current off label use, following scientific advice meetings with the MHRA.

Case Study:

Rituximab in Idiopathic Membranous Nephropathy (IMN)

This single arm study, overseen in partnership with the National Institute for Health and Care Excellence (NICE), is one of eight schemes funded by NHS England to date in which real world data is generated in a NHS setting to inform future front line care and national clinical commissioning policy (funding) decisions. This may provide evidence that is more akin to the results we are likely to see in routine clinical practice than a formal clinical trial.

Rituximab is a biological therapy (or 'biologic') which reduces the number of immune or B cells, which usually help to defend the body against infection. The study focusses on the use of a biosimilar form of Rituximab in the treatment of IMN, an autoimmune disease affecting the kidneys. In this condition the B cells produce harmful autoantibodies which attack the tissues of the kidney and cause inflammation, impacting on their ability to cleanse the blood of toxins and secrete this waste into urine.

Recruitment to the study is now complete (190 patients across 37 renal services) and patients are being followed up over two years to test the drug's effectiveness in achieving disease remission or stabilised / improved renal (kidney) function. The study results are expected to be available for publication in 2022, at which point NHS England will be able to make a formal commissioning decision on whether this un-licensed medicine should be routinely funded in the NHS in the future.

Intellectual Property

47. Intellectual property (IP) can take a wide range of forms, including know-how, data sets, copyright, trademarks and, in some rare cases, patents. It sits alongside research papers or other academic outputs from research. Foreground IP, covering any IP which has been created and/or developed during publicly funded research, including data, is usually owned by the organisation leading research. The owner would however be expected to licence the IP to collaborating partners for non-commercial use.
48. Data are a commercially valuable form of IP, particularly when there is the potential to support regulatory approvals for new products or new indications for existing products (including generics and biosimilars).
49. Written consent would therefore be required for any commercial use of the foreground IP for publicly funded studies, together with a revenue share agreement to meet State Aid requirements.
50. For prioritised medicines, NHS England would consider supporting the generation of new evidence in partnership with commercial partners, subject to the arrangements set out above, where there is potential for it to change clinical practice and / or published clinical

commissioning policy in the NHS in England and where the costs of supply can be met by the company.

Approving for Routine Use

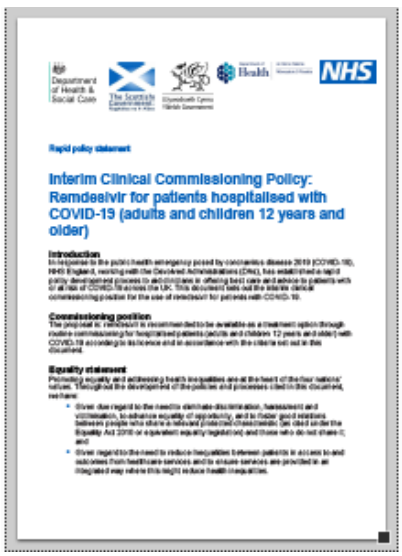
51. NICE produces two forms of guidance which mandate NHS commissioners in England to provide routine funding for the treatments concerned (Technology Appraisals and Highly Specialised Technology Appraisals). However, NICE can only currently develop guidance for medicinal products that either have, or are expected to receive, a marketing authorisation for the indication of interest.
52. NICE has therefore been asked to consider whether it could pilot an adapted approach for off-label medicines so that high quality guidelines can be produced to better inform commissioning decisions.
53. Otherwise, other than for medicines already within NHS tariff arrangements, NHS commissioners (typically clinical commissioning groups (CCGs) or NHS England in one of its national direct commissioning roles, such as specialised commissioning) hold the responsibility for making decisions on which treatments are made available (and funded) within the NHS, including off-label medicines. Decisions will be based on the available evidence of relative clinical benefit and relative cost.

Case Study:

Research to Access Pathway for Investigational Drugs for COVID-19 (RAPID-C19)

RAPID-C19 is a multi-agency initiative, chaired by NICE, which aims to ensure effective treatments for COVID-19 are available to patients quickly and safely. The Oversight Group maintains a horizon scan of UK and international trials building evidence for new (usually 're-purposed') treatments for COVID-19.

Where sufficient positive trial evidence becomes available, Group members help identify the most appropriate regulatory route to enable routine access to the new treatment within the NHS. Collaboration between NHS England and Improvement and the devolved nations, combined with expert clinical advice from clinicians with direct experience of providing care to COVID positive patients in hospital and intensive care, has enabled UK wide clinical commissioning policy decisions to be made within days and to be communicated quickly to front line clinicians through the MHRA Clinical Alerting System (CAS). Lessons from this approach will be directly applicable to the Repurposing Programme going forward.



Rapid policy statement

Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older)

Introduction

Commissioning position

Equality statement

54. The multi-agency RAPID-19 Oversight Group approach (see case study below) has ably demonstrated the opportunity to collaborate between agencies, and between countries, to achieve rapid access to evidence based repurposed medicines.

55. CCGs are responsible for making funding decisions for their local populations, and routine commissioning decisions on off label medicines falling within CCG commissioning responsibilities may therefore vary across England according to local needs and priorities. Although it is not appropriate for NHS England to mandate local off label medicines policy decisions, it can develop a template commissioning policy for discretionary review and adoption by CCGs, particularly in areas where individual clinician decisions on off label use are more challenging (for example in primary care, where specialty specific expertise and experience in using a particular off label medicine may not be available). This approach would ensure that CCG funding prioritisation and decision making is not fettered, but also avoid potential duplication by completing a 'do once' policy drafting process. NHS England has published 35 clinical commissioning policies to date covering medicines in off label use (see Appendix 2).

Opportunities for NHS England

International Context

56. The repurposing challenge is not unique to the UK. Groups have been established in the United States (FDA and Friends of Cancer Research) and the European Union (EC STAMP) to progress repurposing. The MHRA has been closely involved in the EU programme. Both the UK and EU are following similar principles, but the UK is currently more advanced: the MHRA has conducted a pilot scientific advice meeting with two potential candidate repurposing molecules and the British Generics Manufacturer Association (published in Nature Reviews Clinical Oncology) and is considering the value of real-world data for different regulatory approvals. There is therefore a real opportunity for the UK to lead on repurposing. This may include using the Early Access to Medicines Scheme (EAMS) to support sponsors with their development plan and the potential to collect real-world data during the scheme to generate further evidence for the future licensing application.

57. As the single largest national commissioner of specialised services globally, NHS England is in a unique position to lead and partner with other health economies where this helps to identify and progress repurposing opportunities. This includes opportunities to lead clinical commissioning policy development and collaborating on new evidence generation by establishing multi-country or other international studies (for example if patient numbers in an individual country are too small to achieve a powered study) and potentially using the flexibilities offered by the EU exit to establish UK based pilot approaches.

Facilitating Identification, Development and Adoption

Identifying Opportunities / Horizon Scanning

58. A number of candidate medicines have already been identified by charities and others involved in the drafting of the original AMRC report; and following further discussion a number of pilot topics have been identified for the forward off label medicines programme. Early discussions with charities have indicated a high level interest in both identifying further potential candidates for a future off label medicines report and in supporting (in some cases directly) future market authorisation applications.

59. NHS England also has well established access to specialty and programme based expert clinical advice, as well as operating at a whole health economy level. It is therefore in a unique position to build on the opportunities identified through its policy formation role by

working with key partners in the statutory, third sector and pharmaceutical industry to identify potential candidates for future licencing.

60. Moving forward, it will be more appropriate to move towards a more systematic approach to gathering intelligence on potential repurposing opportunities, and early discussions have begun on adding repurposed medicines to the future horizon scanning work of NIHR's Information Observatory. The NIHRIO, based in Newcastle, looks to identify medicines, devices and diagnostics that are up to ten years from being publicly available to help inform policy and research activity.

61. Factors in identifying further priorities may include:

    - The potential to meet a significant, and currently unmet, clinical need
    - The opportunity to significantly improve clinical outcomes and / or patient experience
    - The degree of support of clinicians and patient groups for the proposal
    - The quality of the supporting evidence available (or generatable)
    - The potential for realising savings to the NHS, and wider economy
    - The likely scale and deliverability of the repurposing opportunity, including an appropriate focus on medicines for rarer conditions which may be under-represented under the current commercial environment

Providing a Route Map

62. Once candidate medicines have been identified, it is important to quickly identify the most appropriate path to achieve delivery of the identified benefits, be that the licensing of the product or the publication of national policy or guidance that will support equitable access and adoption. Collaborative work between programme member organisations in securing routes to support adoption of repurposed medicines in the treatment of COVID-19 has enabled significant collective learning in this area. A draft route map, which we would aim to test and refine through the forward work programme, is attached as Appendix 1.

Supporting Clinicians in Their Prescribing Choices

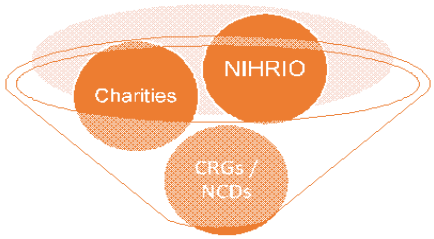
63. The British National Formulary (BNF) is produced and published jointly by the British Medical Association (BMA) and Royal Pharmaceutical Society (RPS) and aims to reflect current best practice as well as legal and professional guidelines relating to the use of medicines.

64. BNF Publications has agreed to ensure that clinical commissioning policy decisions taken, and notified, by NHS England are promptly reflected in published (and electronic / on-line) versions of the BNF to support clinical prescribing decisions.

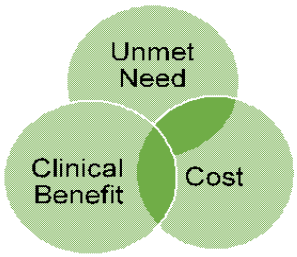
Abbreviations and Acronyms

AMRC	Association of Medical Research Charities
BGMA	The British Generic Manufacturers Association represents and promotes the interests of UK based manufacturers and suppliers of generic medicines
BNF	British National Formulary
DHSC	The Department of Health and Social Care
EMA	European Medicines Agency is responsible for the scientific evaluation of centralised marketing authorisation applications (MAA). Once granted by the European Commission, the centralised marketing authorisation is valid in all European Union (EU) Member States, Iceland, Norway and Liechtenstein.
HMRC	Her Majesty's Revenue & Customs is a non-ministerial department, acting as the UK's tax, payments and customs authority
HST	Highly specialised technologies evaluations are obligatory recommendations on the use of new and existing highly specialised medicines and treatments within the NHS in England
MHRA	The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK
NICE	The National Institute for Health and Care Excellence
NIHR	The National Institute for Health Research is the largest funder of research in the UK and works with partner organisations (including the NHS, universities and industry) to promote and deliver high quality research that can advance scientific innovation, transform front line care and promote economic growth in the UK.
OLS	The Office of Life Sciences champions research, innovation and the use of technology to transform health and social care.
TA	Technology appraisal guidance; recommendations on the clinical and cost-effectiveness of medicines and treatments in the NHS, placing a funding obligation on NHS commissioners in England.

Appendix 1



Potential Repurposing Candidates



Prioritised Candidates

Equitable Access Options

NICE	Licencing	Policy
Guidance / Guidelines	EAMS Innovative Licencing Pathways Full or Conditional Market Authorisation	NHS Clinical Commissioning Policy CCG Template Policies UK Wide Policy CAS Alerts

Appendix 2

NHS England's Published Routine Clinical Commissioning Policies and Policy Statements for Off Label Medicines

Commissioning Policies

- Anakinra to treat periodic fevers and autoinflammatory diseases (all ages)
- Anakinra/tocilizumab for the treatment of adult-onset Still's disease refractory to second-line therapy (adults)
- Bendamustine with rituximab for first line treatment of advanced indolent non-Hodgkin's lymphoma (all ages)
- Bendamustine with rituximab for first line treatment of mantle cell lymphoma (all ages)
- Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages)
- Commissioning medicines for children in specialised services
- Dexrazoxane for the prevention of anthracycline induced cardiomyopathy in children (under 18) receiving anthracyclines for the treatment of cancer
- Eculizumab in the treatment of recurrence of C3 glomerulopathy post-kidney transplant (all ages)
- Gemcitabine and capecitabine following surgery for pancreatic cancer (all ages)
- Metreleptin for congenital leptin deficiency (all ages) (effective from 1 April 2019)
- Plerixafor for stem cell mobilisation in adults and children
- Prescribing of cross-sex hormones as part of the gender identity development service for children and adolescents
- Rituximab and anti-neutrophic cytoplasmic antibody associated vasculitis
- Rituximab as a second line agent for the eradication of inhibitors in patients with acquired haemophilia
- Rituximab for cytopaenia complicating primary immunodeficiency
- Rituximab for immunobullous disease
- Rituximab for immunoglobulin G4-related disease (IgG4-RD)
- Rituximab for second line treatment for anti-NMDAR autoimmune encephalitis
- Rituximab for the treatment of dermatomyositis and polymyositis (adults)
- Rituximab for the treatment of relapsing steroid sensitive nephrotic syndrome
- Rituximab for the treatment of steroid resistant nephrotic syndrome in paediatric patients
- Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies
- Sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis
- Temozolomide for patients with grade 3 anaplastic astrocytoma of the brain (all ages)
- Tocilizumab for Takayasu arteritis
- Treatments for graft versus host disease following haematopoietic stem cell transplantation

Policy Statements

- Alemtuzumab for treating relapsing-remitting multiple sclerosis – third cycle (all ages)
- Antivirals for adults with recent onset (acute) hepatitis C
- Bedaquiline and delamanid for multi-drug resistant TB
- Biologic therapies for the treatment of juvenile idiopathic arthritis

- Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer
- Ivacaftor and tezacaftor/ivacaftor for cystic fibrosis
- Pembrolizumab for drug-resistant gestational trophoblastic neoplasia
- Retreatment of chronic hepatitis C infection in adults with advanced or decompensated cirrhosis Rituximab for myasthenia gravis

Appendix 3

Off Label Medicines Programme Board Membership

- National Medical Director - Specialised Services (NHS England) – Chair and Programme SRO *James Palmer*
- Chief Pharmaceutical Officer (NHS England) *Keith Ridge*
- Director for Innovation and Life Sciences (NHS England) *Sam Roberts*
- Commercial Medicines Director (NHS England) *Blake Dark*
- Director of Policy (Medicines and Healthcare products Regulatory Authority (MHRA)) *Jonathan Mogford*
- Programme Director for Medicines and Technologies (National Institute for Health and Care Excellence (NICE)) *Eric Power*
- Deputy Director – Head of Research Faculty, Infrastructure and Growth (Department of Health and Social Care) *Tony Soteriou*
- Director of Medicines and Pharmacy (Department of Health and Social Care) *Elizabeth Woodeson*
- Director of Strategy and Policy, Specialised Commissioning (NHS England) *Gareth Arthur*
- Programme Director (Clinical Strategy) - Programme Lead *Ann Jarvis*
- Clinical Expert Sub-Group Chair *Richard Cattell, Deputy Chief Pharmaceutical Officer, NHS England*

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