North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 30th April 2015
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Prof L Smeeth	NCL JFC Vice-Chair	**(Vice-Chair)**
	Dr R Sofat	UCLH, Consultant Clinical Pharmacologist	
	Dr E Boleti	RFH, Consultant Oncologist	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Ms S Drayan	NMUH, Chief Pharmacist	
	Mr A Dutt	NHS Islington, Head of Medicines Management	
	Dr R Fox	RNOH, DTC Chair	
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management	
	Mr T James	MEH, Chief Pharmacist	
	Dr M Kelsey	Whittington, DTC Chair	
	Ms L Reeves	C&I Mental Health Trust, Chief Pharmacist	
	Ms P Taylor	NHS Haringey, Head of Medicines Management	
	Mr A Shah	RNOH, Chief Pharmacist	
	Ms N Shah	NHS Camden, Head of Medicines Management	
	Ms W Spicer	RFH, Chief Pharmacist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr L Wagman	Barnet CCG, GP	
In attendance:	Dr H Amer	UCLH, Specialist Registrar	
	Dr F Bennett	UCLH, Specialist Registrar	
	Mr P Bodalia	NCL JFC, Lead Pharmacist	
	Ms M Desai	Dietician, RFH	
	Mr E Hindle	MEH, Formulary Pharmacist	
	Mr I Man	WH, Interim Deputy Chief Pharmacist	
	Mrs H Mehta	NMUH, Formulary Pharmacist	
	Ms R Nancy	Dietician, RFH	
	Ms I Samuel	RFH, Formulary Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
	Dr A Stewart	Camden CCG, Clinical Lead Medicines Management	
Apologies:	Dr D Bavin	Camden CCG, GP	
	Dr R Breckenridge	UCLH, DTC Chair	
	Mr TF Chan	BCF, Chief Pharmacist	
	Dr H Taylor	Whittington, Chief Pharmacist	
	Mr A Karr	NCL Procurement Consortia Chair	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Mr J Paszkiewicz	NEL CSU, Prescribing Advisor	

2. Meeting observers

Prof MacAllister welcomed the applicants and observers to the meeting.

3. Minutes of the last meeting

Ms Spicer informed the Committee that SMOF-lipid was not reviewed by the RFH DTC. Mr Bodalia agreed to revisit the notes from the last meeting and correct the website.
[Post-meeting correction: SMOF-lipid was approved at The Whittington Hospital, March DTC]

4. Matters arising

There were none.

5. Declarations of relevant conflicts of interest

None were declared.

6. New Medicine Reviews

6.1 Renavit® for vitamin deficiency in chronic kidney disease (Applicant: Ms R Nandy (RFH); Presentation: Ms I Samuels)

The Committee reviewed an application for the use of Renavit® for vitamin supplementation as part of dialysis in patients with chronic kidney disease.

The Committee reviewed a prospective observational study of adults (n=16,435) undergoing haemodialysis across Europe and USA. The primary aim of the study was to investigate the patterns of water-soluble vitamin use and outcomes associated with their use, specifically mortality and hospitalisation. Large variation by region in the proportion of patients administered water-soluble vitamins was noted, with a low of 3.7% in the UK to a high of 71.9% in the United States. Patient use of water-soluble vitamins was associated with a lower risk for mortality (RR 0.84, CI 0.76 – 0.94; p=0.001). Although not statistically significant, the risk for hospitalisation was numerically lower among patients administered water-soluble vitamins (RR 0.94, CI 0.85 – 1.04; p=0.24).

The Committee noted that the current preparation available on the RFH Formulary is Ketovite®; however, the vitamin content of this preparation is inadequate when compared with the European Best Practice Guideline (2007) and also requires co-administration of folic acid. Renavit is also more convenient to administer as it only requires once daily administration whilst Ketovite requires thrice daily administration. Further, Renavit can be stored at room temperature, unlike Ketovite which requires refrigeration which may be inconvenient for patients, increases the likelihood of unintentional non-adherence, and potentially increases wastage. Renavit is an ACBS approved "Food for Special Medical Purposes (FSMP)" product, indicated for the management of water-soluble vitamin deficiency in patients with renal failure receiving dialysis and as such may be prescribed in the community on an FP10 prescription. With regards to cost, a one month supply (per patient) of Renavit costs £3.75 compared with £9.26 for Ketovite.

Despite the lack of a published randomised-controlled trial definitively establishing the value of vitamin supplementation, the Committee agreed that vitamin supplementation is a low-cost and low-risk intervention. The Committee therefore agreed to include Renavit on the NCL Joint Formulary.

6.2 Beclometasone dipropionate [Clipper®] for Ulcerative Colitis (Applicant: Dr S McCartney (UCLH); Presentation: Ms S Sanghvi)

The Committee reviewed an application for beclometasone dipropionate modified-release oral tablets (BDP) for the management of mild-to-moderate Ulcerative Colitis (UC) in patients not responding to 5-ASA (aminosalicylate) treatment *and* who are unable to tolerate prednisolone. The Committee reviewed 5 studies of varying designs.

The first (Rizzello et al, 2002) was a 4-week, double blind, randomised, placebo controlled study of oral BDP. All patients also received 3.2g daily of 5-ASA for the duration of the study. The ITT analysis (n-119) demonstrated that both treatment groups reached a significant reduction (p=0.001) in UCDAI score, with a mean absolute reduction of 3.7 in the BDP + 5-ASA group, and 3.0 in the placebo + 5-ASA group.

Although the authors reported the results as being statistically significant (p=0.014 between treatments), the absolute difference between the treatments was small (0.7 on a 12-point scale).

The second (Campieri et al, 2003) was a randomised, parallel-group, single-blind study in patients with active mild to moderate UC (UCDAI score 3 - 10) comparing BDP (5mg daily) with 5-ASA (2.4g daily) for 4 weeks. In the ITT analysis (n=133), the mean UCDAI score was significantly reduced in both groups; from 6.10±0.20 to 2.44±0.29 in the BDP group and from 5.29±0.17 to 2.03±0.23 in the 5-ASA group. The percentages of patients in clinical remission (63% vs 62.5%) and with a significant clinical improvement (15.1% vs 11.3%) did not significantly differ between the BDP and 5-ASA treatment groups.

The third study (Nunes et al, 2010) was a retrospective, multi-centre study assessing the efficacy and safety of oral BDP for active UC from post-marketing experience in clinical practice in Spain. Most patients in the study had left-sided or extensive colitis and were on maintenance therapy with oral / rectal 5-ASA when BDP was started. BDP dose was 5mg/day in 88% of patients and mean treatment duration was 6.2±3.8 weeks. The results showed that BDP was associated with remission in 44.4% of patients, response in 22.3% of patients and failure in 33.2% of patients. Patients treated with BDP for more than 4 weeks had lower failure rates than those treated for less than 4 weeks (p<0.02), however, this is outside of its marketing authorisation. The Committee noted that rescue therapy with systemic steroids was required in most patients failing BDP treatment (31.7%).

The fourth study (Papi et al, 2010) was a single-arm study to assess whether a course of oral BDP would be a useful alternative to oral prednisolone as a second-line treatment. All eligible patients were required to be unresponsive to treatment with 5-ASA, defined as failure to achieve clinical remission within 3 weeks of treatment with oral mesalazine at ≥2.4g/day plus topical mesalazine 2-4g/day (± rectal corticosteroids). Patients received BDP 10mg/day for 4 weeks and then 5mg/day for a further 4 weeks. Oral and rectal 5-ASA was maintained at a stable dose throughout the study period. The primary endpoints were (1) the percentage of patients achieving clinical remission with 8 weeks of oral BDP treatment without requiring systemic corticosteroids and (2) the percentage of patients maintaining steroid-free remission for 12 months post BDP therapy. The results showed that after an 8-week course of oral BDP, 75% of patients (48/64; 95% CI 62.6-84.9%) achieved clinical remission without systemic corticosteroids. Of the 16 patients (25%) who failed to enter remission, 11 patients showed no response or worsened and were switched to systemic corticosteroids, while 5 patients showed partial response and achieved remission after a second course of oral BDP. Overall after 8 weeks of treatment with BDP, mean CAI score decreased from 7.4 points (95% CI 6.9-7.8) to 3.0 points (95% CI 2.3-3.7) (p<0.0001). Patients with moderate disease had a lower remission rate than those with mild disease (47% vs 87% respectively; p=0.003; OR = 0.13). One year post BDP 37 patients remained in remission (58%; 95% CI 44.8-70.0%) and 48 patients (75%; 95% CI 62.6-84.9%) avoided systemic corticosteroids for one year. Although the study reported impressive results, the Committee noted a number of study limitations including the lack of a control or active comparator (e.g. prednisolone), the lack of endoscopic outcomes, and the use of higher doses / longer treatment duration compared to the licensed dose.

The Committee found the fifth study (Balzano et al, 2015) to be the most informative as it provided a comparison of the efficacy and safety of BDP with oral prednisolone in patients receiving 5-ASA therapy (up to 3g/day). Subjects were randomised in a double-blind manner to an 8-week non-inferiority study to receive either (Group 1) BDP 5mg daily for 4 weeks then 5mg on alternate days for 4 weeks, or (Group 2) prednisolone 40mg daily for 2 weeks with tapering dose of 10mg every 2 weeks thereafter. The primary endpoint of clinical response at 4 weeks was achieved in 64.6% of patients in the BDP group and 66.2% in the prednisolone group (treatment difference -1.56; 95% CI -13.00 to 9.88, p=0.76). The percentage of patients with a UCDAI score <1 was similar between the groups; 22% in the BDP group and 21% in the prednisolone group (p=0.89). Although the non-inferiority limit of -20% was set fairly high, the results demonstrated comparable efficacy of the two treatments, however, the dosing of BDP was outside of license. Patients with steroid-related AEs and cortisol <150 nmol/l at week 4 were 38.7% in the BDP group and 46.9% in the PD group (p=0.17 between groups). No safety signals were observed in both the groups. The authors concluded that BDP was non-inferior to PD in the treatment of active UC, with a good safety profile in both the groups.

The Committee concluded on close reading of the Balzano manuscript that BDP might be slightly better tolerated than prednisolone (numerically but not significantly) at its licensed dose, this difference is offset by it being slightly less effective (numerically but not significantly), and was more expensive. With respect

to the proposed place in therapy, the Committee were unsure what the definition of 'non-response' to 5-ASA was as it did not appear as though the trials had included patients who were adequately dose optimised (i.e. not a truly refractory group). Lastly, the Committee were unable to perceive a population that would be 'intolerant' to prednisolone but tolerant of another steroid.

The Committee therefore concluded that the availability of BDP for the management of mild-to-moderate UC would only expose the drugs budget to a more costly therapy with no added clinical value and on this basis agreed that beclometasone dipropionate modified-release oral tablets (Clipper®) should not be included on the NCL Joint Formulary.

7. NICE FAQ: Demonstrating compliance with TA and HST guidance

The Committee reviewed a document, published by NICE, on frequently asked questions (FAQ) relating to local formularies. The Committee noted the current NICE position, which includes:

1. The Secretary of State has directed that *"the NHS is required to provide funding and resources for medicines recommended by NICE through its Technology Appraisal (TA) and Highly Specialist Technology (HST) work programme. A period of 90 days from date of publication is permitted to provide the required funding and resources."*
2. In accordance with the Department of Health publication entitled "Innovation, Health & Wealth: Accelerating adoption and diffusion in the NHS" local formulary processes should not seek to duplicate NICE assessments or challenge an appraisal recommendation and must never act as a barrier to the uptake of NICE approved medicines AND all NICE TA / HST recommendations should be incorporated automatically [where clinically relevant] into local NHS Formularies in a planned way that supports safe and clinically appropriate practice.

The NICE FAQ states that "All NICE-approved treatments must be included in local formularies for use in line with the TA or HST recommendations and with no additional restrictions….. If there is more than one NICE-approved medicine for the condition, providers and commissioners must not recommend that any one of them is used routinely in preference to the others (unless an order of preference is stated in the TAs or HSTs). Similarly, they must not recommend that a medicine that has not been assessed by NICE is used routinely in preference to a NICE-approved medicine".

There is also a statement that "Providers or commissioners can suggest to healthcare professionals that a particular medicine is preferred locally. Reasons for this could include cost, if a medicine is cheaper than other options, to reflect local clinical expert opinion or to achieve optimal stock control. However this local recommendation must only be taken into account after a patient and prescriber have discussed all treatment options and only if they have no preference about which medicine they want to use."

The following key points were raised by the Committee as part of an in-depth discussion:

- There was uncertainty regarding the legal status of this document, it being an interpretation of the terms of the NHS constitution. The JFC is aware of the binding nature of NICE TAs, but has taken the view that a hierarchy of treatments provides the most cost-effective therapeutic approach. Cheaper alternatives (usually older drugs that are off patent) with a more established safety record should be first-line options, many of which do not have the backing of a NICE TA.

- The experience of the JFC is that most new drugs offer no therapeutic advantage over existing treatments, and that complex health-economic arguments contained within NICE TAs do little to eliminate therapeutic uncertainty that arise from the absence of direct comparisons within a single trial of older versus newer drugs. Where a TA does not place the use of a new drug in its proper therapeutic context, the JFC has been obligated to do so.

- The JFC has questioned the value to the NHS of NICE performing separate and time-consuming TAs of new me-too drugs from a single class. For example, three separate NICE TAs have recently been published on the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin and each of these drugs is recommended for the treatment of type II diabetes. The JFC has taken the view that the existence of me-too drugs merely provides an opportunity to negotiate reductions in drug pricing by selecting a preferred option. There are rarely efficacy advantages between drugs in the same class, though occasionally unexpected toxicity arises. The FAQ document implies that these virtually identical treatments for diabetes should be available to patients as they have each been approved

by a NICE TA. The FAQ document suggests that NICE expects each of these drugs should be available on formularies and that any formulary preference should only be taken into account after a patient *and* prescriber have discussed all treatment options and only if they have *no preference* about which medicine they want to use. Implementation of such guidance overrides the rational work of Drugs & Therapeutics Committees and Formulary Committees, which have limited pointless inclusion on drug formularies of essentially similar drugs. To have every member of a drug class available adds to the cost of therapeutics, increases wastage through requirement for greater stocks of medicines in pharmacies and increases the risk of drug error by minimising familiarity.

- The JFC took the view that the FAQ document exposed a paradox in the NHS constitution (see Key Principle No. 6) and was inconsistent with other guidance. It contradicts the Department of Health 'Innovation, Health & Wealth' recommendation that NICE approved medicines should be incorporated in a planned way (i.e. within budgetary limits and the space available for maintaining stocks) that supports safe (as is derived from familiarity with a narrow range of drugs) and clinically appropriate practice (as is indicated by the requirement to prescribe in a cost-effective manner which will usually mean using older drugs that are have never been subject to a NICE TA or HST). For the same reasons, the FAQ document runs contrary to the GP contract ("GPs are to ensure the use of NHS resources in a cost-effective manner") and GMC guidance (paragraph 18 of Duties of a Doctor).

- The selection of medicines listed on Formularies should be based on a judgement of the relative efficacy, safety, convenience and cost. Where a NICE TA makes a positive recommendation, the JFC is obligated to ensure that NICEs recommendations are implemented in their proper context, to ensure optimisation of medicine use, patient safety and best use of resources. The JFC took the view that implementation of the FAQ document would merely increase the uptake of new medicines being heavily promoted by the pharmaceutical industry, in a manner that would increase drug costs without patient benefit.

On the basis of the above points, the Committee were unable to support the implementation of this new guidance.

8. Pathway: Parkinson's Disease

Following discussion at the January meeting, Mr Bodalia circulated a revised version to the NCL Formulary Pharmacists for comment. Mr Daff kindly forwarded a copy to the Edgware Memorial Hospital to check consistency with their Formulary as although they are geographically based within NCL the service is commissioned by Central London Community Healthcare NHS Trust. The Committee found the updated version to be consistent with the NCL Formulary and approved the guideline.

9. Pathway: Diabetic Macular Oedema (DMO)

Mr Hindle presented the Committee with a new pathway (flow-diagram) to simplify the preferred choice of treatment for DMO. This pathway has been developed in consultation with the commissioners from NCL and NCL, as well as having been approved by the NCL/NEL Ophthalmology Network. The Committee approved the guideline.

10. Pathway: wet Age-related Macular Degeneration (wAMD)

Mr Hindle presented the Committee with a new pathway (flow-diagram) to simplify the preferred choice of treatment for wet AMD. This pathway has been developed in consultation with the commissioners from NCL and NCL, as well as having been approved by the NCL/NEL Ophthalmology Network. The Committee approved the guideline.

11. Best Practice Guidance: Mesalazine MR

The Committee previously considered and approved a proposal for Octasa® to be the primary mesalazine modified-release preparation across NCL for the management of Ulcerative Colitis (May 2014). Following an analysis of the issue data at CCG level for the 2014-15 period, it appears that Asacol still appears to hold the majority market share (36%), with Mezavant XL in second place (17%) and Octasa trailing behind (9%). Mr Bodalia reminded the Committee that the guidelines from the British Society of Gastroenterology (BSG) and the European Crohn's and Colitis Organisation (ECCO) state that there is limited evidence to suggest any clinically important differences between the different preparations. As such, Octasa represents the most cost-effective treatment, and provides the CCGs an opportunity to

realise significant cost savings. The Committee supported this as a safe therapeutic switch programme provided it was done by a clinician, including GPs. The commissioners agreed to pass the memo on to their GPs.

12. Local DTC recommendations

Site	Drug / Indication	Outcome
BCF / RFH	Cytarabine liposomal for Lymphomatous Meningitis	Approved pending funding confirmation [RFH site only]
	HyQvia (subcutaneous immunoglobulin) for primary immunodeficiency	Approved pending funding confirmation [RFH site only]
	Rituximab for interstitial lung disease	Approved for 2 patients only pending funding confirmation [RFH site only]
	Fosfomycin as last-line treatment for bone, vascular and organ space infections	Approved for 10 patients (restricted to Consultant Microbiologist recommendation) pending funding confirmation
RNOH	Fentanyl patch (12mcg/hr / 25mcg/hr) for acute postoperative pain in primary knee replacement surgery	Approved under Evaluation for 30 patients [RNOH site only]

13. Next meeting

Thursday 28th May, Room 6LM1, Stephenson House, 75 Hampstead Rd.

14. Any Other Business

Mr Daff asked for an update on the NOAC pathway for primary / secondary prevention of VTE and prevention of stroke in AF. Dr Sofat and Mr Bodalia informed the Committee that the NIHR funded Health Technology Assessment are finalising their extensive review and due to submit in May. It is anticipated that an update will be brought to June JFC meeting.