North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Monday 17 September 2018
Room 4+5, Floor 4B, Maple House, 149 Tottenham Court Rd, Bloomsbury, London W1T 7NF

Present:	Dr R MacAllister	NCL JFC Chair	**(Chair)**
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Dr D Hughes	RFL, Consultant Haematologist	
	Dr R Sofat	UCLH, DTC Chair	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Dr M Kelsey	WH, DTC Chair	
	Mr S Semple	MEH, Interim Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Dr R Woolfson	RFL, DTC Chair	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	Ms W Spicer	RFL, Chief Pharmacist	
In attendance:	Mr A Barron	NCL MEP, Lead Pharmacist	
	Dr P Bodalia	UCLH, Principal Pharmacist	
	Ms M Kassam	NCL JFC, Support Pharmacist	
	Mr G Grewal	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
	Ms P McCormick	WH, Lead Pharmacist – Medicine	
	Mr P Aghakhani	WH, Acting Lead Pharmacist – Medicine	
	Ms A Tynan	RFL, Rheumatology Pharmacist	
	Ms H Amer	UCLH, Clinical Pharmacologist	
	Mr J Hartwell	UCLH, Formulary Pharmacist	
	Dr A Singh	RFL, Consultant Rheumatology	
	Dr J Manson	UCLH, Consultant Rheumatology	
	Dr C McNamara	UCLH, Consultant Haematology	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr M Dhavale	Enfield CCG, GP Clinical Lead Medicines Management	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management	
	Prof A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr T Rashid	NHS Haringey, GP Clinical Lead Medicines Management	
	Mr TF Chan	RFL, Deputy Chief Pharmacist	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr F Gishen	RFL, Palliative Care Consultant	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Mr T Dean	Patient Partner	
	Dr A Sell	RNOH, DTC Chair	
	Mr S Richardson	WH, Chief Pharmacist	

2. Meeting observers

Dr MacAllister welcomed Mr Tomlin (GOSH, Chief Pharmacist) as a new member of the Committee and Mr Hartwell (UCLH, Formulary Pharmacist) as an observer to the meeting.

3. Minutes of the last meeting

The minutes and abbreviated minutes were accepted as accurate reflections of the August meeting.

4. Matters arising

4.1 Dequalinium chloride 10mg vaginal tablets for the treatment of bacterial vaginosis - pregnancy

At the August 2018 meeting the Committee approved the use of dequalinium vaginal tablets for the treatment of bacterial vaginosis as a second-line alternative to clindamycin 2% intravaginal cream in patients who have not tolerated or failed metronidazole treatment. This approval included an action for JFC Support to consult with NCL Microbiologists and Gynaecologists to confirm whether clindamycin 2% cream should be removed from the formulary.

Feedback from RFL was that there is limited experience of dequalinium in pregnancy compared to significant evidence of safety of clindamycin 2% intravaginal cream therefore obstetricians would like to keep clindamycin 2% intravaginal cream on formulary.

It was agreed that clindamycin 2% intravaginal cream should remain on formulary, and dequalinium would be an addition to the formulary.

4.2 Fraudulent papers relating to bone density

JFC Support were asked to identify whether any NCL guidelines were affected by the fraudulent papers relating to a bone density researcher identified in a recent article in "Science" magazine .

One guideline has the potential to be affected, 'Calcium + vitamin D supplementation for the prevention of osteoporotic fragility fractures', however a search of the primary and secondary references identified none of the known fraudulent papers were authored or co-authored by Dr Y. Sato.

5. JFC Work Plan & outstanding actions

These items were included for information only. Any questions should be directed to Ms Kassam.

6. Declarations of relevant conflicts of interest

Dr McNamara, Consultant Haematology UCLH, informed the Committee that he has had direct contact with the manufacturers of Anakinra for compassionate use in his private clinic; however he has not received any remuneration for this. The Committee did not consider this to be a conflict.

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Jun-18	Caplacizumab (compassionate access)	Thrombotic thrombocytopenia while available under a manufacturer-funded patient access scheme only	Decision: UCLH only Prescribing: Secondary care only Tariff status: N/A Funding: FOC scheme Fact sheet or shared care required: No
UCLH	Jun-18	Silver Diamine Fluoride	High risk dental caries on primary anterior teeth in children <3 years old or with special needs - second line option where resin sealant or sodium fluoride varnish are not considered appropriate, pending review of the consent form	Decision: UCLH only Prescribing: Secondary care only Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

UCLH	Jul-18	Idebenone EAMS (appeal)	Duchenne's Muscular Dystrophy for patients in active respiratory decline (%FVCp 80-25%)	Decision: UCLH only Prescribing: Secondary care only Tariff status: N/A Funding: FOC via EAMS Fact sheet or shared care required: No
RFL	Jul-18	Patisiran (compassionate access)	Amyloid transthyretin (ATTR) amyloidosis Under FOC EAMS subject to MHRA approval decision	Decision: RFL only Prescribing: Secondary care only Tariff status: N/A Funding: FOC scheme Fact sheet or shared care required: No
RFL	Jul-18	Magnesium lactate SR (MagTab®)	Renal tubular disorders. For use in renal tubular disorders outpatients clinic only	Decision: RFL only Prescribing: Secondary care only Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
GOSH	Jul-2018	Multivitamin (inclusive of Vitamins D, E, K & A - DEKAs Plus®)	For the dietary management of patients with cystic fibrosis on the specific recommendation of a specialist in cystic fibrosis	Decision: Added to NCL Joint Formulary Prescribing: Primary and secondary care Tariff status: In tariff Funding: Trusts and GP budgets Fact sheet or shared care required: No
UCLH	Apr-2007 and Jun-2010	Fentanyl sublingual immediate release tablets	Pain or Palliative Care recommendation only: Treatment of breakthrough pain in adult patients using opioid therapy for chronic cancer pain and receiving palliative care, who are unable to obtain relief from, or are intolerant to, immediate release oral morphine and oxycodone	Decision: Added to NCL Joint Formulary Prescribing: Primary and secondary care Tariff status: In tariff Funding: Trusts and GP budgets Fact sheet or shared care required: No
All	Unknown	Oestrogel® (oestradiol 0.06% w/w)	Hormone replacement therapy for oestrogen deficiency symptoms in postmenopausal women	Decision: Added to NCL Joint Formulary Prescribing: Primary and secondary care Tariff status: In tariff Funding: Trusts and GP budgets Fact sheet or shared care required: No

7.2 **Not approved**

UCLH	Jul-18	Imatinib (off-label)	Unresectable, locally advanced or metastatic pigmented villonodular synovitis (PVNS) or diffuse tenosynovial giant cell tumour (D-TGCT).	Decision: Not Approved

8. **New Medicine Reviews**

8.1 **Anakinra for secondary haemophagocytic lymphohistiocytosis (Kineret; Swedish Orphan Biovitrum Ltd) (Applicant: Dr A Singh [RFL], Dr J Manson [UCLH], Dr McNamara [UCLH])**

The committee considered an application to use anakinra, an interleukin-1 receptor blocker, in the management of haemophagocytic lymphohistiocytosis (sHLH), an under recognized, hyper inflammatory condition with a high mortality. sHLH can be triggered by an autoimmune condition (where it is also known as Macrophage Activation Syndrome [MAS]), malignancy or infection. Current management varies according to underlying cause; rheumatology practice entails steroids ± intravenous immunoglobulin ± ciclosporin, whereas haematology practice commonly follows the HLH-2004 protocol of dexamethasone, methotrexate, etoposide and ciclosporin.

The evidence to support anakinra is based on case series, case reports and one post-cohort analysis of a randomised controlled trial in patient with sepsis features of sHLH. Survival at follow-up was reported in 61 of the 71 cases reported in literature. Anakinra was reported as well tolerated; injection site reactions were documented most frequently and one case of pancytopaenia following administration of a higher dose (8mg/kg/day). The committee heard that in most case reports and case series, anakinra is typically administered in combination with corticosteroids with the addition of ciclosporin, or other treatment in some cases, and has been shown to be successful in the treatment of sHLH when steroids ± IVIG has failed to control disease. Most publications describe subcutaneous administration of anakinra at a dose of 100mg once or twice a day; however higher doses of anakinra or IV administration are reported in one retrospective study and in a few case reports. IV administration may be necessary in ITU when patients are oedematous or have absorption issues. 12 cases of sHLH treated with anakinra in UCLH and RFL were also presented to the committee; 4 deaths were reported and a variation in anakinra dosing was noted.

The main adverse events reported with anakinra are blood dyscrasias (including neutropenia and thrombocytopenia) and an increased risk of infections however NCL consultants report anakinra to be safe where sHLH occurs in the context of concurrent infection.

The committee heard from Dr McNamara (Haematology) that patients present extremely unwell and aim of treatment is to keep patients alive whilst the underlying haematological malignancy is diagnosed. Anakinra is particularly useful in this setting as anakinra does not compromise diagnostic accuracy and has low toxicity profile. Anakinra is stopped once treatment with chemotherapy has been initiated, estimated after 3-6 months of treatment with anakinra.

The Committee heard from Dr Singh (RFL) that anakinra was preferred early in the treatment pathway, Day 2 onwards, in order to minimise the use of steroids which themselves have problematic adverse effects, including infection. Dr Manson (UCLH) expressed hesitancy using anakinra without corticosteroids, due to the lack of evidence. Clinical experts agreed that the duration of anakinra was hard to estimate as there is no guidance on how to wean patients off anakinra; tapering usually occurs cautiously once persistently low ferritin levels and cytopaenia have responded. The consensus was that higher doses may be required in the acute setting with low doses (100 to 200mg) continued in the ambulatory setting for 2 to 6 months. Patients with rheumatological conditions for which anakinra is routinely commissioned (e.g. Stills disease and Juvenile Idiopathic Arthritis [JIA]) would continue on anakinra in the long-term.

The estimated budget impact for anakinra for sHLH was £176,000 per annum across NCL, based on an average dose of 200mg daily for 6 months. Canakimumab, an alternative IL-1 antagonist, in place of anakinra was deemed inappropriate due to longer duration of action (4 weeks vs. 1 day), lack of supportive evidence, and increased cost.

In camera, the Committee agreed that the available evidence-base supported the use of anakinra for sHLH. The Committee requested that consultants agree on the most appropriate dose, route and duration of treatment which should be integrated within the NHSE policy development application. Where use of anakinra for sHLH is required in advance of NHSE funding approval, individual Trusts should develop local protocols (to include place in therapy [relative to steroids and IVIg], dosing range, route of administration, duration of treatment and stopping criteria) which would support clinical staff and be used to estimate the budget impact for internal funding approval until NHSE funding is obtained.

Action: Rheumatology and haematology consultants to agree within their services on the most appropriate dose, route and duration of treatment anakinra for the treatment of sHLH. This information will be incorporated into the Trust's budget impact assessment and the NHSE policy development application. Where use of anakinra for sHLH is required in advance of NHSE funding approval, individual Trusts should develop local protocols (to include place in therapy [relative to steroids and IVIG], dosing range, route of administration, duration of treatment and stopping criteria) which would support clinical staff and be used to estimate the budget impact for internal funding approval until NHSE funding is obtained

Decision: Clinically approved, pending funding approval
Prescribing: Secondary care only
Tariff status: Excluded from tariff however not routinely funded for this indication.
Funding: Hospital funded at present; local DTC / high-cost medicine panel to oversee each patient request. Application to NHSE to be submitted.
Fact sheet or shared care required: No
Additional information: Evidence to support SC or IV (local practice is to administer in 100mL sodium chloride 0.9%w/v over 1 hour).

8.2 Human papilloma virus vaccine (Gardasil®) for MSM in line with Public Health England national immunisation schedule

The Committee considered an application for the use of a quadrivalent vaccine effective against Human papilloma virus (HPV) vaccine types 6, 11, 16 and 18 (Gardasil®) for the prevention of HPV infection in Men who have Sex with Men (MSM) up to and including the age of 45. This will be offered opportunistically in HIV and GUM clinics in line with a Public Health England (PHE) national immunisation schedule.

Giuliano et al (n=4065) reported a placebo-controlled, double-blinded, randomised, international multi-centre trial, comparing a complete schedule of Gardasil with an equivalent schedule of placebo for safety and efficacy against HPV infections. A sub-study was carried out in the MSM population (n=602). Gardasil administration resulted in a significant reduction in observed external lesion relating to all four HPV types of 65.5%, with an observed reduction of 70.2% in the MSM sub-study. In the secondary efficacy outcomes, a reduction of 47.8% of persistent infections associated with all four HPV types was observed, with 43.6% reduction observed in the MSM group. The weaknesses of the study include the exclusion of participants who are likely to contract HPV (such as those who have had more than five sexual partners), and excluding participants who would be eligible for the vaccination based on their age (i.e. those aged 9-15, and those from the upper age limit of their respective sub-group up to and including 45 years of age). The strengths come from the study design and the use of sample and power calculations.

In terms of safety, the majority of side effects relate to the administration of the injection (e.g. injection site reactions, headaches, pain in the extremities, pyrexia, haematoma or pruritus). The budget impact to NCL is negligible because the vaccine is free of charge from PHE for use in line with the national vaccination programme.

A query was raised whether or not GPs would be able to offer this vaccination in primary care. However, the immunisation programme is designed such that all vaccinations given to eligible patients should be recorded on surveillance systems available in GUM and HIV clinics. This would therefore not be suitable for primary care administration. In summary, Gardasil for use in line with PHE recommendations for their immunisation schedule in MSM patients aged up to 45 years was approved.

Decision: Approved
Prescribing: Secondary care only (restricted to GUM and HIV clinics in line with PHE recommendations)
Tariff status: Free of charge vaccine
Funding: Free of charge vaccine
Fact sheet or shared care required: No

8.3 Modified FOLFIRINOX for adjuvant treatment of pancreatic cancer (Applicant: Dr R Gillmore, RFL)

The Committee considered an application for the use of modified FOLFIRINOX (mFOLFIRINOX) treatment (consisting of oxaliplatin, irinotecan, 5-fluorouracil and folinic acid) in the adjuvant setting following macroscopic resection of pancreatic adenocarcinoma. The modifications to the protocol are a reduction in the dose of irinotecan (from 180mg/m^2 to 150mg/m^2), and the removal of a bolus dose of 5-fluorouracil.

Evidence for the protocol comes from a trial which is currently only available in abstract. Conroy et al (n=493) reported a randomised, multi-centre, phase III trial comparing the mFOLFIRINOX protocol (given every fortnight for a total of 24 cycles) against gemcitabine alone (given once a week for 3 weeks, followed by a week break, for a total of 24 weeks). The study was performed with patients who had histologically proven pancreatic adenocarcinoma with complete macroscopic resection (graded as R0 or R1) aged 18-79 years, who have not have had any previous radiotherapy or chemotherapy, have a WHO

performance status of 0 or 1, and should have fully recovered from their curative resection surgery so they can start treatment within 21-84 days post-operatively. There was a reported improvement in the primary efficacy outcome of disease free survival, with a median increase of 8.8 months (HR = 0.59). Median overall survival, a key secondary outcome, also increased by 19.6 months (HR = 0.66). Limitations of the evidence were that the data was only available as an abstract and that the comparator, gemcitabine monotherapy, is not standard-of-care (SOC) for this indication. Current SOC is gemcitabine in combination with capecitabine (GEMCAP) in line with favourable results from the ESPAC-4 trial, and as such mFOLFIRINOX has not been directly compared to SOC. The hazard ratio for overall survival for mFOLFIRINOX compared to gemcitabine (HR = 0.66) is lower than that for GEMCAP compared with gemcitabine (HR = 0.82), therefore mFOLFIRINOX is likely to be superior to GEMCAP/SOC in terms of efficacy.

Grade 3 or 4 adverse events were found to be higher in the mFOLFIRINOX group, though rates of adverse events were the same in both arms at 12%. There was no difference in neutropaenia or anaemia in both arms but there was higher GCSF usage in the mFOLFIRINOX arm. mFOLFIRINOX had significantly higher rates of diarrhoea, and it also led to more nonsignificant occurrences of peripheral neuropathy, fatigue, vomiting and mucositis than gemcitabine alone. mFOLFIRINOX users suffered from thrombocytopaenia, headache, fever and flu-like syndrome, though at a lower rate than the gemcitabine arm.

The estimated impact to the NCL is around £1,000 per patient, which for the 10 patients estimated in NCL equates to around £10,000 per annum. A query was raised as to whether the treatment would be funded by NHS England; as FOLFIRINOX is already funded by NHS England, the modified version would also be funded.

It was acknowledged that the increase in survival would be associated with an increased in adverse effects and subsequently a decrease in quality of life and the patients should be made aware of this as part of the informed consent process. In summary, the Committee agreed to add mFOLFIRINOX to the NCL Joint Formulary as adjuvant therapy following macroscopic resection of pancreatic adenocarcinoma.

Decision: Approved
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: NHSE
Fact sheet or shared care required: No

8.4 Evidence review to support 5th line high-cost therapies for rheumatoid arthritis (Applicant: Prof M Ehrenstein, UCLH)

The committee considered an application for fifth line high-cost therapies for rheumatoid arthritis (RA) *in absentia*. The committee heard that an NCL pathway was approved in 2014 which incorporates four biologics, one per mechanism of action. Since 2014 a new class of medicines, Janus Kinase inhibitors (JAKi), have become available which opens the possibility of a fifth different mechanism of action to be made routinely available.

The Committee heard that data from JAKi were most likely to include patients who had already been exposed to other lines of treatment; however a systematic search of the literature found no case reports or case series of JAKi (or other drug) used fifth line. A number of meta-analyses and studies reported improvements in RA disease activity in patients who had previously had inadequate response to biological DMARDs prior to enrolment into the studies. The primary evidence included RA-BEACON and ORAL STEP, two randomized, double-blind, placebo-controlled clinical trials. Both trials randomised patients with moderate to severe RA with insufficient response to one or more TNF inhibitor into one of three arms: placebo or one of two JAKi doses. The primary outcome was the ACR20 response. Subgroup analysis of RA-BEACON reported that 53% (24/45) of patients who had received ≥3 prior biological DMARDS experienced clinical improvement at 12 weeks with 4mg OD baracitinib dose. Likewise a post-hoc analysis of ORAL STEP reported 41.7% (5/12) of patients who received ≥3 prior anti-TNFs experienced clinical improvement at 12 weeks with 10mg BD tofacitinib dose.

Audit data of 7 UCLH patients on ≥4 lines of therapy were presented to the committee; 3/7 (43%) had a good response to treatment (DAS > 1.2), 3/7 (43%) had a weak response to treatment (DAS < 1.2 or no DAS score available with subjective description of some response), and 1 patient discontinued tocilizumab due to diverticulitis.

The Committee noted that treatment for RA is life-long and the alternative to fifth line therapy would be corticosteroids. Long-term use of steroids is associated with osteoporosis which is especially problematic in patients with pre-existing joint disease. The committee discussed that introducing a new mechanism has significant budget impact considerations, however fifth line therapy is clinically valid. As the number of patients on 4th line therapy is unknown the budget impact across NCL was estimated at £330,000 cumulative per annum.

The Committee agreed there is an unmet need in the treatment of patients that have failed, unable to tolerate, or had contra-indications four lines of biologics. Whilst the published literature did not specifically address the efficacy of therapies used in the 5th line setting, the available evidence supported a view that a new mechanism used early in the treatment pathway was as effective as that same new mechanism used later in the pathway. By extension, if high-cost therapies are cost-effective early in the treatment pathway, they would remain cost-effective later in the treatment pathway. The Committee determined that JAKi were beneficial at any line of the RA pathway; the benefit of oral agents as first-line for needle-phobic patients was noted.

In summary the Committee agreed adding a 5th mechanism of action to the NCL RA pathway was likely to be a cost-effective use of resources. The decision would be referred to NCL Commissioners (CCGs and NEL CSU) for funding consideration.

Decision: Clinically approved, pending funding approval.
Prescribing: Secondary care
Tariff status: Excluded from tariff
Funding: CCGs
Fact sheet or shared care required: No

9. Direct oral anticoagulant (DOAC) counselling checklist update

The counselling checklist had undergone minor amendments by UCLH and RFL co-authors. The amendments were approved and the updated document would be uploaded to the NCL website.

10. 'Best value biologic' implementation policy for North Central London

The Committee considered a new policy in North Central London regarding the use of Best Value Biosimilar (BvB) medicines. The policy included three key points:

- The decision of which licensed biologic to be used by provider trusts will be based on the biosimilar contract or framework produced by LPP
- From the date of a framework or contract being available for a biosimilar medicine, this should be prescribed in preference to the originator. As such, it is expected that 100% of new patients will be prescribed the best value biosimilar
- From the date of a framework or contract being available for a biosimilar medicine, all existing patients will undergo transition to the biosimilar medicine within 8-12 weeks (excluding applications to the local BSG)

The Committee approved the policy and suggested that it be ratified at each local DTC for adoption.

Action: Policy to be disseminated to local DTCs to enable local implementation.

11. Guideline: Managing Common Infection in Primary Care in North Central London

The guideline, which has come through JFC previously, has undergone additional amends therefore was put forward for approval.

Dr Kelsey noted that the advice for Pelvic Inflammatory Disease (PID) describes the compulsory testing of *Mycoplasma genitalium* however most local laboratories cannot test for this. The guideline was otherwise approved.

Action: Dr Kelsey and Mr Barron to update the PID monograph as required.

12. Should adalimumab be the preferred first-line biologic for psoriasis?

The Committee reviewed the draft prescribing pathway for high-cost drugs in psoriasis. The pathway proposes the use of ustekinumab *or* adalimumab as options for first-line therapy for severe psoriasis. This is inconsistent with JFC recommendations from June and July 2017 which recommends first-line adalimumab as the most cost-effective treatment option. If ustekinumab is desired as first-line therapy, a formal appeal to the JFC is required.

Action: Commissioners to contact providers to request adalimumab is used as first-line therapy

13. **Next meeting**

Monday 15th October 2018, 16:30 – 18:30, LG01, 222 Euston Road, Kings Cross, London, NW1 2DA.

14. **Any other business**

- The Committee heard from Dr Urquhart that NHSE had concerns about the rising costs and limited supplies intravenous immunoglobulins in England. To manage this, NHSE has recommended the creation of sub-regional IVIG panels. An expression of interest has been submitted on behalf of NCL in the guise of a sub-committee of JFC. The Committee agreed that this was useful and the proposal for a sub-regional IVIG panel for North Central London was agreed.

- Mr Tomlin (GOSH) queried how haemophilia products are evaluated and distributed at other NCL sites. Ms Spicer advised RFL take all haemophilia products through their DTC for approval, although stock is held by respective haemophilia teams.