North Central London
Medicines Optimisation Network

Joint Formulary Committee (JFC): Minutes

Minutes from the meeting held on 17th November 2022

		Present	Apologies
Prof A Hingorani	NCL JFC Chair	✓	
Dr B Subel	NCL JFC Vice Chair		✓
Ms G Smith	RFL, DTC Chair		✓
Ms W Spicer	RFL, Chief Pharmacist	✓	
Dr A Scourfield	UCLH, DTC Chair	✓	
Mr J Harchowal	UCLH, Chief Pharmacist	✓	
Dr R Urquhart	UCLH, Divisional Clinical Director	✓	
Dr K Tasopoulos	NMUH, DTC Chair	✓	
Ms S Stern	NMUH, Chief Pharmacist		✓
Dr M Kelsey	WH, DTC Chair	✓	
Mr S Richardson	WH, Chief Pharmacist	✓	
Dr S Ishaq	WH, Consultant Anaesthetist	✓	
Dr A Worth	GOSH, DTC Chair		✓
Ms J Ballinger	GOSH, Chief Pharmacist	✓	
Mr S Semple	NCL ICS, Interim Chief Pharmacist; GOSH, Interim Chief Pharmacist		✓
Mr A Shah	RNOH, Chief Pharmacist	✓	
Prof A Tufail	MEH, DTC Chair		✓
Ms N Phul	MEH, Chief Pharmacist		✓
Ms K Delargy	BEH, Chief Pharmacist	✓	
Ms L Reeves	C&I, Chief Pharmacist		✓
Dr L Waters	CNWL, Consultant Physician in HIV		✓
Ms R Clark	NCL ICB, Head of Medicines Management (Camden)		✓
Mr P Gouldstone	NCL ICB, Head of Medicines Management (Enfield)	✓	
Ms E Mortty	NCL ICB, Interim Head of Medicines Management (Haringey)	✓	
Ms M Singh	NCL ICB, Head of Medicines Management (Barnet)	✓	
Mr A Dutt	NCL ICB, Head of Medicines Management (Islington)	✓	
Dr D Roberts	NCL ICB, Clinical Director (Islington)	✓	
Mr T Dean	Patient partner		✓
Ms S Amin	IPMO Programme Team, JFC Principal Pharmacist	✓	
Mr G Grewal	IPMO Programme Team, JFC Support Pharmacist	✓	
Ms I Samuel	RFL, Formulary Pharmacist	✓	
Mr H Shahbakhti	RFL, Formulary Pharmacist	✓	
Mr A Barron	UCLH, Principal Pharmacist	✓	
Mr S O'Callaghan	UCLH, Formulary Pharmacist	✓	
Mr A Stein	NMUH, Deputy Chief Pharmacist	✓	
Ms A Sehmi	NMUH, Formulary Pharmacist	✓	
Ms K Mistry	RNOH, Formulary Pharmacist	✓	
Ms H Thoong	GOSH, Formulary Pharmacist	✓	
Mr D Sergian	MEH, Formulary Pharmacist	✓	
Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	✓	
Ms A Fakoya	NCL ICB, Contracts & Commissioning Pharmacist		✓

Dr A Hosin	UCLH, Clinical Pharmacology Registrar	✓	
Ms EY Cheung	NCL ICB, Deputy Head of Medicines Management (Camden)	✓	
Dr A Hosin	UCLH, Clinical Pharmacology Registrar	✓	
Ms M Thacker	RFL, Clinical Lead Pharmacist	✓	
Prof D Ralph	UCLH, Consultant Urologist	✓	
Miss P Sangster	UCLH, Consultant Urologist	✓	
Prof G Conway	UCLH, Consultant Endocrinologist	✓	
Ms D Joshi	UCLH, Specialist Pharmacist	✓	
Prof D Thorburn	RFL, Consultant Hepatologist	✓	
Dr N Halliday	RFL, Consultant Hepatologist	✓	
Ms R McGaw	RFL, Specialist Pharmacist	✓	

2. Meeting observers and members

Prof Hingorani welcomed members, applicants and observers to the meeting (see above).

3. Members' declaration of interests

Declarations of interests register was included for information. Professor Hingorani declared that he was an author on one of the papers relating to agenda item 10. No other interests relevant to the agenda were declared, and no further declarations were raised by members or attendees.

4. Minutes of the last meeting

Minutes and abbreviated minutes of the November 2022 meeting were circulated to Committee members for comments. Due to the late circulation, the minutes will be ratified via Chair's action pending any further comments from the Committee.

5. Matters arising

5.1 Licensed metolazone 5mg tablets (Xaqua®) implementation strategy

In October 2022, the Committee discussed the newly licensed metolazone product (Xaqua®) which has double the bioavailability compared to the previously used unlicensed product. The Committee agreed that criteria for starting or switching to Xaqua should be created and presented back at the next meeting. Colleagues from RFL supported in providing suggested criteria:

- NCL Trusts should initiate new patients on Xaqua®
- Patients receiving unlicensed metolazone in NCL primary care should be referred back to their specialist to oversee the switch to Xaqua® and monitor until stable before primary care continues prescriptions again
    - NCL GPs should be advised to prioritise referrals for the cohort of patients receiving unlicensed 5mg metolazone first
    - Patients receiving unlicensed 2.5mg metolazone who are required to switch to Xaqua® (e.g., due to availability of the unlicensed product) should have their reviews staggered back to their specialist due to capacity issues

The Committee were supportive of the proposed criteria and approved the implementation advice for dissemination to local teams.

5.2 Hyperemesis treatment pathway

In September 2022, the Committee considered an application for Xonvea® (doxylamine and pyridoxine) for hyperemesis gravidarum. The Committee requested that a pathway was developed to support implementation of Xonvea® on to the NCL Joint Formulary. JFC Support worked with the applicant to develop a pathway to outline the treatment options and place of prescribing for local implementation in NCL Trusts, which was presented back to the Committee.

Overall the Committee was supportive of the pathway and noted that recommendations made aligned with those previously suggested previously by the Committee. The Committee requested an additional footnote be added with respect to the appropriate duration of metoclopramide which is otherwise suggested for a maximum duration of 5 days. The Committee also requested that generic medication names are used instead

of brand names. The Committee approved the pathway pending these minor changes and approved the addition of Xonvea® to the NCL Joint Formulary in line with the recommendations in the pathway.

Medication: Xonvea® (doxylamine and pyridoxine)
Decision: Added to the NCL Joint Formulary
Prescribing: Secondary care initiation, primary care continuation
Tariff status: In tariff
Funding: Trust and ICB
Fact sheet or shared care required: No
Additional information: NCL Trusts to incorporate recommendations in the JFC pathway into local guidance to support local implementation in local Trusts

6. Review of action tracker

Action tracker included for information.

7. JFC Outstanding Items & Work Plan

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

8. Local DTC recommendations / minutes

8.1 Approved

DTC site	Date	Drug	Indication	JFC outcome
NMUH	Jun 2022	Febuxostat	Prophylaxis of Tumour Lysis Syndrome in adults with haematologic malignancies	**Decision:** Added to the NCL Joint Formulary **Prescribing:** Secondary care **Tariff status:** In tariff **Funding:** Trust **Factsheet or shared care required:** N/A
RFL	Jun 2022	FOC scheme: Lenalidomide*†	Relapsed or refractory B-cell or T-cell lymphoma	**Decision:** Added to the NCL Joint Formulary **Prescribing:** Secondary care **Tariff status:** N/A – Free of charge **Funding:** N/A – Free of charge **Factsheet or shared care required:** N/A
UCLH	Oct 2022	Human Papillomavirus 9-valent vaccine (Gardasil 9®)	Severe recurrent respiratory papillomatosis	**Decision:** Added to the NCL Joint Formulary **Prescribing:** Secondary care **Tariff status:** In tariff **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Patient outcome data to be collected and reported back to the Committee
UCLH	Sept 2019	Imatinib tablets	Pigmented villonodular synovitis/ tenosynovial giant cell tumour PVNS/T-GCT	**Decision:** UCLH only **Prescribing:** Secondary care **Tariff status:** In tariff **Funding:** Trust **Factsheet or shared care required:** N/A

8.2 Approved under evaluation

DTC site	Month	Drug	Indication	JFC outcome
RFL	Sep 2022	Lanreotide*	Small bowel angioectasia	**Decision:** RFL only **Prescribing:** Secondary care **Tariff status:** Not routinely commissioned **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Approved clinically; subject to a new investigational procedure application. Outcomes from the audit to be presented to RFL DTC within one year

† The relevant commissioner should be notified in line with NCL Free of Charge scheme guidance. Approval is conditional on the provision of a free of charge scheme agreement and funding statement. * Subject to funding consideration.

8.3 Alopecia treatments on the NCL Joint Formulary

The Committee was presented with a request to add additional information to alopecia drugs on NetFormulary to demonstrate their status for primary care prescribing. The Committee agreed it was appropriate to indicate those medicines which are listed in Part XVIIIA of the Drug Tariff (medicines which should not be ordered under the General Medical Services contract).

8.4 Use of cenobamate in NCL

The Committee considered the use of cenobamate in centres across NCL in line with NICE TA753. The wording used in the NICE TA states that treatment should be started "in a tertiary epilepsy service", as cenobamate is recommended at the point in the pathway where patients are referred for review by a tertiary specialist. Tertiary services exist at RFL and NHNN, although epileptologists from NHNN also work in other centres such as NMUH; should they wish to commence cenobamate, they are currently required to refer to themselves at their NHNN service before treatment can commence.

The Committee agreed that the current wording of a "tertiary epilepsy service" as the service being provided by an epilepsy specialist, rather than the physical location where it was being offered. The Committee discussed other aspects which need to be considered by the DGH service prior to implementation, such as specialist pharmacist competency, restriction to tertiary consultants and shared learning on the transfer of prescribing responsibility once stabilised. JFC Support will work with NMUH to support implementation.

Decision: Added to the NCL Joint Formulary
Prescribing: Secondary care initiation, primary care continuation
Tariff status: In tariff
Funding: Trust and ICB
Fact sheet or shared care required: Yes – deferred to the NCL Shared Care Group to update the cenobamate shared care

9. New Medicine Reviews

9.1 Appeal: Clomifene for symptomatic male hypogonadism for adults desiring to preserve fertility (Appellant: Miss P Sangster, UCLH)

The Committee considered an appeal for clomifene (up to 50mg once daily), a selective oestrogen receptor modulator, for the off-label indication of symptomatic male hypogonadism in adult men who wish to preserve fertility. The Committee had previously considered clomifene for this indication in 2016 where it was rejected on the following grounds: i) despite an improvement in biochemical markers there was no evidence it improved symptoms of hypogonadism, ii) concerns were raised that body weight was not described in trials or the proposed treatment algorithm, and iii) the clinician who attended JFC to support the application proposed it would be used to improve semen parameters and increase the success rate of microsurgical testicular sperm extraction (microTESE), which differed from the indication outlined in the original application

The treatments currently available on the NCL Joint Formulary include testosterone and human chorionic gonadotrophin (HCG). However, testosterone was stated to cause reduction in sperm concentration which impacts fertility, and HCG requires twice weekly injections which impacts compliance. International or national guidance does not currently list clomifene as a treatment option. The EMA have reviewed enclomifene (the active isomer of clomifene) for hypogonadotropic hypogonadism in adult men with BMI≥25 kg/m^2 wishing to

preserve testicular function and spermatogenesis; the EMA did not approve enclomifene owing to a lack of evidence which could sufficiently translate to clinically meaningful benefits, concerns of representativeness in studies, and an increase in VTE risk.

The appeal was made to use clomifene as a first-line pharmacotherapy option (after lifestyle interventions) on two grounds. The first was that the original decision was based on inaccurate or incomplete information, as the clinician who attended the JFC meeting in 2016 provided incorrect information; the intended use of clomifene is to improve hypogonadal symptoms only, and not to improve semen parameters or increase the success rate of microTESE.

The second ground for appeal was that significant new information was available which required reconsideration of the evidence. Three studies were submitted for reconsideration. The first focused on medical empirical therapy for idiopathic male fertility, and hence was not reviewed further as the outcomes of interest were not aligned with the application. The second study by Kim et al was a report on two 16-week, double-blind study to compare the efficacy and safety of enclomifene, Androgel (testosterone gel) and placebo for male patients aged 18-60 years with BMI 25-42kg/m^2 and secondary hypogonadism (n=256). The primary endpoint, the pooled number of subjects with a normal testosterone level, was significantly better with enclomifene compared to Androgel (63.5% vs. 24.7% [p<0.001]). In one of the secondary outcomes, the change in mean sperm concentration in those who used enclomifene was not significantly different [p=0.91], though those who used Androgel had a significantly reduced sperm count [p=0.01]. Key limitations of the study were that symptomatic hypogonadism was not an inclusion criterion, lifestyle interventions were given alongside pharmacotherapy rather than before, and there was a lack of description of the randomisation, allocation or cohorts who discontinued treatment.

The third study was one which was not previously considered by the JFC. Krzastek et al was a retrospective review in two institutions in patients receiving clomifene for hypogonadism. Patients were included if they opted to receive clomifene with a testosterone level <300ng/dL (n=400). In one of the outcomes, 366 patients (92%) achieved testosterone >300ng/dL, and 303 patients (76%) had an increase in testosterone of 200ng/dL from their baseline level. In other outcomes, patients were assessed using the ADAM questionnaire (Androgen Deficiency in Ageing Males); of 389 evaluated patients, 305 (78%) reported an improvement, and there were no differences between subgroups using clomifene <3 years and those receiving ≥3 years. Key limitations were that the study was retrospective with no comparator, ADAM scores were not quantified (and hence there is uncertainty around the degree of improvement), patients who were excluded were not quantified, and only 41% of patients met the American Urology Association target testosterone range of 450-600ng/dL.

In terms of safety, Krzastek et al found clomifene was linked with adverse effects in 36 patients (9%), including mood changes, blurred vision, nipple tenderness, weight gain and acne. 14% of patients required anastrozole due to an increase in oestradiol which was found to be significantly higher in individuals who used clomifene ≥3 years versus <3 years (24% vs 11% [p<0.001]). The EMA review found enclomifene caused an increase in thromboembolic events compared to testosterone (4 incidents versus 0 incidents). In terms of budget impact, clomifene is expected to save up to £63,000 per annum in 100 patients compared to HCG.

The Committee heard from Miss Sangster, Prof. Ralph and Prof. Conway that the typical patient cohort who will benefit from clomifene are younger males, and only around 10% of hypogonadism seen cases are obesity related. The clinicians were aware that the available evidence did not report well on symptom improvement and the likelihood of robust RCTs being conducted in the future is unlikely. The improvement in sperm count was considered to translate well to fertility although this would be an extrapolation. The clinicians offered the opportunity to collect further data via an evaluation of selected outcomes, due to the lack of available data particularly around the risk of VTE incidence. The use of clomifene prior to HCG would be considered a useful addition to the formulary as it would offer an oral medication which can improve compliance, would reduce the number of referrals to the endocrine team (who are the only team who can initiate HCG currently), and would reduce the number of times patients need to attend hospital who currently have HCG initiated there.

In camera, the Committee discussed whether an RCT would be feasible as it would be the ideal way to gather more data rather than a local evaluation. The Committee found it difficult to make a positive recommendation for a medication that has had previous rejections from both the FDA and EMA. Importantly, there was a lack of clarity in the application about the *precise* indication(s) for clomifene, in which patients and the precise goal of therapy. The committee felt that the application could not be taken further without these points and corresponding the supporting evidence being clarified and addressed. Therefore a decision was made to

request further information on these issues from the appellants, in addition to any further information on comparative information vs HCG as clomifene would be displacing it as the first-line pharmacotherapy.

In summary, based on the evidence available and the lack of clarity of certain elements of the proposed evaluation, the Committee could not recommend the use of clomifene. Therefore, the Committee requested that further information is provided to steer the Committee for a final decision, including:

- Clear initiation criteria
- Clear specification of the patient cohort
- Comparative evidence of clomifene vs HCG
- The exact outcome data proposed for collection in any evaluation
- Stopping criteria
- Details on the outcomes of interest and how the outcome data will be collected
- The formulary status in other London ICS areas

Decision: Deferred

9.2 Appeal - Proprems to prevent necrotizing enterocolitis in premature neonates

Following a request from the appellants, the appeal was deferred to a future JFC meeting.

9.3 Rapid reviews for DMARDs used for autoimmune hepatitis

The Committee considered rapid reviews for several DMARDs (mercaptopurine, mycophenolate and methotrexate) for off-label use for autoimmune hepatitis and to consider addition into current NCL interface documents to aid transfer of prescribing and monitoring to primary care where appropriate.

Summary	
Drug	Mercaptopurine, Mycophenolate and Tacrolimus
Indication	Autoimmune hepatitis
Formulation/Route	Oral tablets/capsules (liquid formulations if appropriate)
Dose	Mercaptopurine: 0.5-1mg/kg/day Mycophenolate: 500mg BD, titrated according to response to max 1.5g BD Tacrolimus: 2mg BD, adjusted according to LFT response (lowest effective dose used); aim for tacrolimus level 5-10 and doses adjusted accordingly
Legal status and procurement	Legal status: POM Storage & handling requirements: Cytotoxic
Patient cohort	Adults
Requesting site	RFL (tertiary hepatology service)
Efficacy	All rated as **AMBER**
Safety	Mercaptopurine and Mycophenolate – **AMBER** Tacrolimus – **AMBER/RED**
Funding route and cost	• In tariff • Mercaptopurine 50mg OD tablets = £144 per patient per annum • Mycophenolate 1g BD tablets = £168 per patient per annum • Tacrolimus 2mg BD capsules = £1,621 per patient per annum • Costs may differ based on formulation used (increase in cost associated with solutions and suspensions)

Estimated impact	• Budget impact:
	  ○ Mercaptopurine – not used regularly but if replacing azathioprine, 50mg OD would cost £12,838
	  ○ Mycophenolate – 1g BD in 33 patients would cost £5,540
	  ○ Tacrolimus – 2g BD in 63 patients) would be £102,097
	• Requires long term monitoring and prescribing as proposed to move to primary care following specialist initiation and dose stabilisation in line with existing DMARD factsheet

Other considerations	• Monitoring requirements • Tacrolimus currently retained in hospital; not in any NCL interface document; requires stabilisation by specialist and will require tacrolimus blood level monitoring.

	• Proposed treatment pathway: o High-dose steroids +/- azathioprine for induction o Mercaptopurine used as an alternative 1st line to azathioprine for intolerance o Mycophenolate as a 2nd line option o Tacrolimus as a 3rd line option

The Committee heard from Dr Halliday that there are high quality studies associated with azathioprine and corticosteroids in RCTs, though for other treatments the evidence is generally retrospective and with low patient numbers. However, this has informed national and international guidance in which there is good consensus for the use of these DMARDs. There is a current RCT comparing mycophenolate with azathioprine in a head-to-head study, though outcomes are awaited. Although mercaptopurine is listed as an alternative to azathioprine, this is only in patients who have had an intolerance; patients who have poor response to azathioprine generally do not respond well to mercaptopurine. Dr Halliday acknowledged that tacrolimus may not be appropriate for primary care prescribing, and hence the intention is to retain prescribing within the RFL service.

In camera, the Committee considered the addition of mercaptopurine, mycophenolate and tacrolimus for autoimmune hepatitis were appropriate additions to the Joint Formulary and agreed that tacrolimus should be restricted to secondary care only due to the risk of adverse effects and blood monitoring required. The Committee requested that data from the active RCTs are brought back to the Committee when they publish.

In summary, the Committee agreed to add mercaptopurine (as an alternative to azathioprine when it is not tolerated), mycophenolate (second-line treatment) and tacrolimus (third-line treatment; secondary care only) to the NCL Joint Formulary for the treatment of autoimmune hepatitis.

Medication: Mercaptopurine and Mycophenolate for autoimmune hepatitis
Decision: Added to the NCL Joint Formulary
Prescribing: Secondary care initiation, primary care continuation
Tariff status: In tariff
Funding: Trust and ICB
Fact sheet or shared care required: Deferred to the NCL Shared Care Group to update the NCL DMARDs quick reference guide

Medication: Tacrolimus for autoimmune hepatitis
Decision: Added to the NCL Joint Formulary
Prescribing: Secondary care only
Tariff status: In tariff
Funding: Trust
Fact sheet or shared care required: N/A

10. Comparative efficacy and safety or DOACs for atrial fibrillation

During development of the NICE guideline for the management of atrial fibrillation (AF), the guideline committee considered a network meta-analysis which found apixaban had the highest probability of being the most cost-effective first line therapy for atrial fibrillation. However, following stakeholder consultation, the NICE AF guideline committee concluded that the network meta-analysis was flawed and could not be included as part of the evidence base for the final guideline, leading to the conclusion that all DOACs were considered equal. Following this, a national DOAC procurement exercise identified edoxaban as having the lowest acquisition cost, and NHSE published commissioning recommendations placing edoxaban as the first line DOAC for non-valvular AF where clinically appropriate. In addition, an Investment and Impact Fund indicator giving preference to edoxaban was released.

The Committee discussed the recent publication of three recently published cohort studies investigating the comparative efficacy and safety of DOACs, the largest of which was an international population-based cohort study which covered 221 million people who were newly diagnosed with atrial fibrillation. All three studies found positive associations with the use of apixaban compared with other DOACs in either efficacy outcomes, safety outcomes or both. These data are consistent with the network meta-analysis rejected by NICE,Queries were raised by the Committee as to how the outcomes in this new evidence may impact the NICE AF guidance

and therefore the NHSE commissioning recommendations. The Committee agreed to write to both NICE and NHSE to escalate these queries.

11. Evusheld position statement

The Committee considered a position statement for Evusheld®, a combination of two monoclonal antibodies for the pre-exposure prophylaxis of COVID-19. The UK Government has decided not to procure Evusheld® for use in NHS patients in advance of the planned review by NICE for a technology appraisal. The Committee were informed that there have been requests made to formulary teams for Evusheld®, and to avoid a position of inequity a position statement has been drafted to align with UK Government advice. The Committee were in support of the recommendations and approved the position statement.

12. Next meeting

Thursday 15th December 2022

13. Any other business

Recall of teicoplanin

The Committee discussed the recent recall of teicoplanin due to the presence of bacterial endotoxins. This was a class 1 recall (i.e., immediately remove affected stock and contact patients who had been issued the impacted batches). The Committee acknowledged it would be difficult to identify which batches had been previously administered to patients. Individual NCL Trusts had already acted on the alert and would be further discussed in the relative safety committees.