North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 25th June 2015
Room 6LM1, Stephenson House, 75 Hampstead Rd

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

2. Meeting observers

Prof Smeeth welcomed the applicants and observers to the meeting.

3. Minutes of the last meeting

Item 7.5 (paragraph 6), an incorrect reference to rituximab was made. The sentence should be amended to state that "The Committee approved the use of *sildenafil and bosentan* in line with the criteria for commissioning within NHS England Clinical Commissioning Policy A13/P/e for Trusts that are eligible to access the policy."

The minutes were otherwise accepted as an accurate record of the meeting.

4. Matters arising

Item 4 (NICE FAQ: Demonstration compliance with TA and HST guidance) – This action is in progress. Mr Bodalia is awaiting feedback from other London networks.

Item 6 (Vitamin D Guideline) – Dr Khan has been invited to the August meeting.

Item 7.1 (Melatonin for sleep disorders) – Dr Quinlivan has been invited to the August meeting.

Item 7.2 (Secukinumab for plaque psoriasis) – Questions relating to the proposed commissioning criteria were answered within the NICE FAD which was published on 27th June.

Item 7.4 and 7.5 (NHSE funded drugs) – Mr Bodalia has been informed by the Pharmacy Lead for NHSE Specialised Commissioning that each NHS Trust currently signed up to the Deferred Tariff Option (emergency tariff) must provide NHSE with their commissioning intention (via their Supply Manager) for each new Commissioning Policy that they wish to access.

The Committee questioned whether a log of outstanding actions was kept. Mr Bodalia informed the Committee that a tracker of all applications since 2012 has been created and that the deferred / pending actions points will be addressed following a prioritisation exercise.

5. Declarations of relevant conflicts of interest

Ms L Reeves and Mr P Gouldstone both declared that they had participated in advisory boards for lurasidone.

6. New Medicine Reviews

6.1 Mesenchymal stem cells for treatment of osteogenesis imperfecta (Applicant: Dr A David, UCLH; Presentation: Mr P Bodalia)

The Committee reviewed a joint application between UCLH and GOSH for the use of human fetal mesenchymal stem cells (hfMSC) for the treatment of osteogenesis imperfecta (OI). The JFC welcomed Dr Shangaris (Specialist Registrar, Obstetrics and Fetal Medicine) who attended the meeting on behalf of the applicant.

The Committee heard that OI is a very rare condition characterised by low bone mass and increased fracture risk. There are four types that are characterised by collagen mutation (type I to IV). Type I is the mildest and most common, types II and III are the most severe, and type IV is the most clinically diverse. Current management includes physiotherapy, orthopaedic surgery and treatment with bisphosphonates; there is currently no approved treatment for this condition. A recent Cochrane review highlighted that bisphosphonates only show improvement to bone mineral density and impact on reducing fractures is unclear.

The proposed application relates to use of hfMSC as a 1st line prenatal treatment for women who have a foetus with a confirmed molecular prenatal diagnosis of severe OI (type III or severe type IV), where the mother has declined termination of pregnancy. Post-natal treatment will then be delivered to the child up to twice annually until age 18 years. Where children are diagnosed with type III or severe type IV disease post-natal, they will also receive treatment up to twice annually until 18 years of age. Prenatal treatment

will occur at UCLH and postnatal treatment will take place at GOSH. It is proposed that use of hfMSC is expected to reduce the need for the above non-curative management interventions.

The Committee was advised that the rationale for delivering transplantation prenatally include reducing the risk of fatal fracture during delivery and the potential for better engraftment rates during the foetal development process. The Committee was also informed that following donor extraction, the hfMSC will be expanded prior to implantation, which means this form of treatment is likely to fall into the category of an Advanced Therapy Medicinal Products (ATMP). The unit that produces the stem cells is based in Sweden and holds a licence for manufacturing ATMPs.

The Committee reviewed the available data for this treatment, noting that it was limited to three case reports, all outside of the UK.

- Patient A was treated in Sweden. Following confirmed diagnosis of OI, *in utero* transplantation was conducted at week 32 with no signs of foetal distress. The child was delivered at 35 weeks. At months 0, 7 and 9, no immune reaction to transplantation was noted. At month 4 the child developed a compression fracture of the spine and was started on IV pamidronate. During the first two years, three fractures were experienced, but there was no impairment of psychomotor development or growth velocity. Between 2 and 8 years of age, multiple fractures and compression fractures were experienced and growth rate slowed. A decision was made to give annual post-natal infusion of hfMSC from the same donor. The child is now 13 years old and has experienced no further fractures.
- Patient B was treated in Singapore. Following confirmed diagnosis of OI, *in utero* transplantation was conducted at week 31 with no signs of foetal distress. The foetus experienced no new fractures and the child was delivered at 38 weeks. There were no signs of immune response to the transplant. Bisphosphonate therapy was given from one month age. This child received her first post-natal transfusion at age 1.5 years. Post-infusion, growth velocity has improved and the child has started to walk; specific details of the current clinical picture are unavailable.
- Patient C (lives in Ireland) was treated in Sweden. Following confirmed diagnosis of OI, *in utero* transplantation was conducted at week 28 with no signs of foetal distress. The child was delivered at week 37 via Caesarean section. This child experienced a fractured femur at birth, but has had no other fractures since. This child is currently one year of age and awaiting the one year postnatal transfusion.

The Committee were informed that the cost of hfMSC and associated infusion is £7,194 (per infusion), however this treatment is currently available free-of-charge under funding agreement with the Swedish Medicines Agency. A Europe-wide clinical trial protocol is under development with UCLH and GOSH listed as participating sites; recruitment will be dependent upon formal approval, which is not likely to be until January 2016 at the earliest.

The Committee explored the inclusion criteria specified within the application, which appeared to be:

- Individuals who have already received an *in utero* transfusion and are due a postnatal injection (1 patient)
- Individuals who have a molecular diagnosis of OI and reach week 28 prior to clinical trial recruitment (2 patients)
- Individuals who receive a postnatal diagnosis of OI and will therefore be excluded from the trial
- Individuals who do not consent to participate in the clinical trial

The Committee heard from Dr Shangaris that evidence of MSC transplantation in animal studies suggests that this intervention results in a reduction in fracture rates in mild to moderate OI. The Committee was advised that there is currently ethics approval in place for delivery of the hfMSC in Sweden on a compassionate use basis. The 3 patients identified will fall outside of the clinical trial inclusion criteria and are thus the key individuals within this application. Lastly, as far as Dr Shangaris is aware, administration of hfMSC will be covered under ethics approval for prenatal blood transfusion / amniocentesis, which is routine procedure at UCLH.

The Committee questioned how inpatient costs outside the clinical trial will be dealt with and who will be responsible for paying these. Dr Shangaris advised that for patients who are not UK residents, agreements will be made with their home country to ensure all costs are covered. For UK patients, funding will be

obtained through increased tariff activity. The Committee suggested that these should be treated as Individual Funding Requests for each CCG, as treatment could go on until 18 years of age.

On reflection of the available data, the Committee felt that this treatment was clearly innovative and fulfils an unmet need for a serious, debilitating condition, however, there is a paucity of human data and thus still appears to be at the early stages of a clinical trial. As such it would not be appropriate for individuals to receive treatment outside of a clinical trial setting whilst a clinical trial is open. With reference to the proposed inclusion criteria, the Committee were supportive of off-trial treatment under compassionate use for the one patient (patient C) who has already received a prenatal transfusion and now requires postnatal treatment on the basis that this individual would not meet the inclusion criteria for the clinical trial. For the other proposed inclusion criteria within the application, as treatment has not yet been provided to these individuals the Committee agreed that they would like to see the information that parents had been given before they could made a decision.

In summary, the Committee agreed that off-trial access to hfMSC for the treatment of OI could only be supported under compassionate-use for the one patient due a postnatal dose (patient C) restricted to the UCLH / GOSH specialist centres, pending clarification with the MHRA on how this would be imported. The Committee agreed that use in patients prior to the clinical trial opening should be deferred to the next meeting where the applicant is invited to explore the patient consultation process.

Action: Mr Bodalia to invite Dr David to the next meeting.

Action: Mr Minshull to contact the MHRA to confirm that approval has been received for importation of hfMSC from Sweden.

Action: Mr Minshull to contact NHSE to clarify commissioning intensions for this specialist service / treatment.

6.2 Lurasidone for schizophrenia (Applicant: Dr V Kirchner, C&I MHT; Presentation: Mr J Minshull)

The Committee reviewed an application for the use of lurasidone, a second generation antipsychotic that inhibits effects of dopamine and 5-hydroxytryptamine, in adult patients with schizophrenia for whom weight gain and/or metabolic disturbance is, or has the potential, to be problematic, and for whom aripiprazole has not been effective. This is on the basis of concern with currently available therapies for schizophrenia being associated with an increased risk of metabolic abnormalities. The Committee was advised that the requested use was for a more restricted place in the treatment pathway than its product licence.

The Committee was advised that, in addition to the evidence provided by the applicant, the London Medicines Evaluation Network (LMEN) has recently completed a review of lurasidone, suggesting it as an alternative for subjects in whom weight gain and metabolic adverse effects would be considered a problem, however, not recommending it for subjects with treatment-resistant schizophrenia. The Scottish Medicines Consortium has also reviewed the evidence and cost-effectiveness of lurasidone and approved it for use in NHS Scotland as an alternative for patients with schizophrenia in whom it is important to avoid weight gain and metabolic effects.

The evidence base for lurasidone consists of three 6-week, double-blind RCTs (one with a 12-month blinded extension study), a double-blind withdrawal study, and a comparative study with risperidone in clinically stable schizophrenic patients. Inadequate response to a second generation antipsychotic due to metabolic effects was not pre-specified as a patient group in these clinical trials. The Committee noted that aripiprazole is the main comparator to lurasidone, however, there are no head-to-head studies comparing these two drugs. On review of the data, although the Committee noted that the CHMP reported lower potential for metabolic effects and no profound impact on QTc prolongation associated with lurasidone, the Committee found that the incidence of adverse events were similar to other second-generation antipsychotics (e.g. EPS, nausea, sedation/somnolence, moderate prolactin increase, hypersensitivity reactions). Although fewer patients taking lurasidone experienced clinically meaningful (≥7%) weight gain than those taking quetiapine (4% vs. 15%), olanzapine (4-8% vs. 34%), the Committee were unconvinced of the clinically meaningful threshold used as the mean absolute increase in weight was in the order of 0.43 kg in the pooled short term clinical trials. The Committee further noted that lurasidone had a higher rate of akathisia compared with quetiapine (13% vs. 2%), risperidone (14% vs. 8%) and olanzapine (12 – 23% vs. 7%).

The Committee focussed their review on a table from the EMA Assessment Report for lurasidone which showed that 7.4% (46/624) of patients reported weight gain on lurasidone compared to 5% (4/85) of patients taking quetiapine MR; 5% (32/624) of patients taking lurasidone reported weight loss, compared with 2.4% (2/85) of patients taking quetiapine MR and 4.5% (9/199) of patients taking risperidone. Thus, the Committee concluded that there is a potential for more weight gain with lurasidone compared with quetiapine MR.

The Committee moved on to the cost-effectiveness analysis provided to the SMC, which presented a base-case analysis of lurasidone compared with aripiprazole. Although the analysis found that lurasidone was dominant to aripiprazole (less expensive and more effective) this was based on a small increase in quality-adjusted life-years (QALYs) of 0.005 and a cost saving of £3,864. A secondary comparison with quetiapine also found lurasidone to be dominant. The cost savings were driven by a reduced relapse rating requiring less intervention. In an additional economic case provided by the company, lurasidone was found to be cheaper but no more effective than aripiprazole, however the Committee acknowledged that this benefit may no longer stand as aripiprazole is no longer under patent protection and cheaper generics are currently coming to market.

Lastly, the Committee reviewed the results of a mixed-treatment meta-analysis (Leucht et al, Lancet 2013; 382:951-962) which was not included as part of the submission. This paper reviewed the evidence for safety and efficacy of 15 oral antipsychotic drugs including lurasidone (212 RCTs; n=43,049) within their Marketing Authorisation. The key findings were that all antipsychotics are significantly more effective than placebo for the primary efficacy outcome (mean overall change in symptoms). Interestingly, the Committee noted that in the Forest plot comparing efficacy of the 15 antipsychotics with placebo, lurasidone was ranked second to last. In the Forest plot for all-cause discontinuation, lurasidone was ranked third worst (olanzapine, aripiprazole and quetiapine all ranked better than lurasidone) and was found to be poorly tolerated due to extrapyramidal effects (similar to chlorpromazine and risperidone, less well than olanzapine, quetiapine and aripiprazole). Finally, lurasidone was ranked as least likely to affect QT interval and had one of the best effects on weight when compared to placebo (similar to haloperidol).

The Committee noted from the application that in practice patients tend to cycle between antipsychotics as there is often inter-patient variability. The Committee however did not feel that there was sufficient data to show that lurasidone would be effective in the refractory group of patients identified.

In summary, the Committee agreed that lurasidone should not be added to the NCL Formulary for the above indication.

6.3 Idelalisib for first line P53 deleted chronic lymphocytic leukaemia (CLL) (Applicant: Dr Cwynarski; Presentation: Mr K Thakrar)

This item was deferred to the next meeting as there were a number of questions that needed clarification from the applicant before the nominated presenter could adequately convey the application to the Committee.

Action: Mr Thakrar to invite Dr Cwynarski to the next meeting

6.4 Tolvaptan for polycystic kidney disease (Applicant: Dr D Gale; Presentation: Ms S Sanghvi)

The Committee reviewed an application for the use of tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD), an inherited condition marked by the growth of numerous fluid-filled cysts in the kidneys and other organs. The Committee welcomed Dr Daniel Gale (Consultant Nephrologist).

Tolvaptan is the first licensed treatment option for this condition. The Committee was advised that ADPKD is a severely debilitating condition that leads to an impaired quality of life. Approximately 50% of patients experience associated destruction of the renal parenchyma. ADPKD is the fourth leading cause end stage renal disease in adults. The purpose of tolvaptan is to slow the progression of cyst development and renal insufficiency in patients. In ADPKD, the kidney cells do not respond appropriately to vasopressin. Tolvaptan blocks vasopressin receptors in the kidney, regulating fluid balance and slowing cyst formation.

The Committee noted that NICE is currently undertaking a Technology Appraisal assessment of tolvaptan for this indication, and have recently published an Appraisal Consultation Document (ACD) which found that the ICER is above the usual NICE threshold and therefore do not recommend. Without approval from NICE, this treatment is unlikely to be funded by NHS England.

The Committee reviewed the key double-blind, placebo-controlled phase 3 RCT (TEMPO 3:4). This trial randomised 1,445 patients in a 2:1 ratio to receive either tolvaptan (n=961) or placebo (n=484). Patients were required to have an eGFR > 60mL/min to participate in the trial. The primary end point in the trial was the rate of total kidney volume change from baseline. Although subjects receiving tolvaptan reported a statistically significant relative reduction in total kidney volume of 49.2% over three years when compared to placebo; the Committee noted that the absolute volume reduction was only 2.7%.

On review of the safety and tolerability outcomes, the Committee noted that adverse events most commonly associated with tolvaptan as reported in this trial were thirst (55% patients), polyuria (38%), nocturia (29%) and pollakiuria (23%). Serum ALT and AST elevations were also reported, as were infrequent elevations of bilirubin. The discontinuation rate of treatment was 23% in the tolvaptan group compared to 14% in the placebo group. The Committee were surprised that subjects taking tolvaptan were required to drink up to 6 L of water daily to counter the side-effects would impact on tolerability and reduce the risk of exacerbating renal impairment; Dr Gale informed the Committee that the treatment elicits a strong thirst response and as such believed that the side effects will lead patients to drink, even 6 L, therefore they will always remain hydrated.

Dr Gale explained to the Committee that the indication for treatment is not kidney enlargement, but declining kidney function, which was measured as a pre-specified secondary endpoint. Data are available to 8 years showing tolvaptan reduces the rate of progression of kidney function, with a very significant delay in onset of end-stage renal disease if the correct patients are chosen. As RFH is a leading centre for nephrology, Dr Gale is already treating 10 patients as part of a clinical trial. He explained that polyuria and polydipsia are on-target effects of the drug; when renal function drops below a particular rate, patients can no longer feel impact of this due to reduction of nephrons.

The Committee questioned if there were any stopping criteria and were advised that CKD 5 (ESRF) would be an indication for stopping. Dr Gale advised the Committee that there is a transitory reduction in GFR when the drug is initiated, but this returns soon afterwards. Dr Gale also clarified that he does not anticipate using this drug in patients on haemodialysis. The Committee asked whether there is any robust evidence of the economic impact of using tolvaptan in this indication to prevent the need for dialysis; however Dr Gale explained that in order to power a clinical trial using dialysis or death as an endpoint, it would need to be conducted over decades which is not practical.

On the basis of its pharmacology, the Committee discussed whether tolvaptan exerted its activity through its impact on blood pressure rather than a direct effect on vasopressin. Dr Gale did not believe this was the effect as tolvaptan is considered an ineffective antihypertensive; pharmacological effect in this condition is thought to be due to cAMP activity in renal cysts.

The Committee noted that tolvaptan for kidney disease is currently undergoing the NICE TA process [ID652] with anticipated publication in September and therefore asked Dr Gale the rationale for the submission ahead of publication date. Dr Gale explained that there are a number of patients he wants to treat in advance of the NICE decision and will be able to access the drug free of charge ahead of this. Dr Gale explained to the Committee that the impact of delayed treatment in patients with PKD is significant because onset is typically in adults in their 50s and thus at the key earning period of life as well as supporting elderly relatives and children at University. The Committee was advised that the application is for the treatment of up to 40 patients at RFH if national funding is put in place.

The Committee were unable to determine the true value of tolvaptan, particularly as it was compared against placebo with no reference to standard of care. The Committee were also unsure of the generalisability of the trial data as the inclusion criteria was limited to adults under 50 years of age and therefore excluded the population targeted within the application. Further, on review of the trial patient profile, the Committee noted that a large number of patients enrolled were ineligible to receive treatment with the number of patients at CKD stage 3 being relatively small at 17%. The Committee also raised concern with the choice of primary endpoint, total kidney volume, questioning its relevance on the

basis that it is a surrogate marker. Lastly, the Committee noted the summary of the NICE ACD, where the Evidence Reference Group failed to establish the true benefit of tolvaptan compared with placebo based on the Tempo 4:3 trial.

In summary, the Committee agreed that tolvaptan should not be added to the NCL Formulary for the above indication but should wait for the outcome of the NICE Technology Appraisal Assessment.

6.5 Octreotide LAR for polycystic liver disease (Applicant: Dr D Gale; Presentation: Ms S Sanghvi)

The Committee reviewed an application for the use of octreotide acetate long-acting release (LAR) injection as first-line treatment for polycystic liver disease (PLD).

The Committee were informed that PLD is a rare genetic condition. It can occur either as an extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD) or solely in the liver (autosomal dominant polycystic liver disease, ADPLD). Symptoms of PLD are progressive and can result in an enlarged liver that compresses the gastrointestinal tract, inferior vena cava, portal vein and bile ducts. Symptoms of the condition include early satiety, gastro-oesophageal reflux, abdominal distention, lower back pain, hypotension, inferior vena cava thrombosis, hepatic venous outflow obstruction ascites, dysponea and jaundice. Liver failure does not seem to be an experienced symptom. To date, there have been no pharmacological treatments for this condition, and management has been through liver resection and hepatic transplant. Octreotide is a somatostatin analogue, which antagonises cAMP and reduces secretion of fluid into hepatic cysts. The prescribing of octreotide LAR for PLD represents an off-label indication (i.e. does not hold a Marketing Authorisation for PLD).

The Committee noted that the proposed place in therapy is for patients with a diagnosis of ADPLD, ADPKD or autosomal recessive polycystic kidney disease (ARPKD) with symptomatic enlargement of liver cysts who are likely to require transplant in the next 5 years.

The Committee reviewed the published evidence, which is limited to two small RCTs and one extension study. In the larger double blind, placebo-controlled RCTs (n=42), patients were randomised (2:1) to receive either octreotide LAR or placebo for one year. The primary outcome measured was percentage liver volume change at one year compared to baseline. Secondary outcomes measured included kidney volume change, kidney function and quality of life (QOL). There was a significant reduction in liver volume in subjects receiving octreotide LAR compared with subjects receiving placebo (-4.95% ± 6.77% with octreotide LAR, compared to +0.92% ± 8.33% with placebo, p=0.048), with the absolute change in liver volume in the treatment arm reducing from 5908 ml ± 2915 ml to 5557 ml ± 2659 ml. The Committee noted that subjects with larger livers at baseline experienced a larger reduction in liver volume, however, this was considered to be as expected. The Committee also noted that subjects in the octreotide LAR arm had larger baseline liver volumes, which may bias the treatment effect in its favour, although this was not reported to be statistically significant. Subjects receiving octreotide LAR also reported a significant reduction in some QOL aspects (physical role and body pain).

In the smaller prospective RCT, twelve patients received either octreotide LAR 40 mg or placebo. Although the primary end point was kidney growth, the authors conducted a *post-hoc* analysis considering reduction in liver volume as the primary endpoint; this was significantly reduced with octreotide LAR compared to placebo (-71±57 ml vs. +14±85 ml, p<0.05).

A one-year, open-label extension study of the larger RCT (n=41) measured total liver volume as the primary end point. A number of secondary end points, such as change in kidney volume, glomerular filtration rate and quality of life were also measured. Patients who had received placebo during the double-blind phase received octreotide LAR during the open-phase. One patient from the octreotide LAR arm in the original study did not continue to the open-label study and a further patient was excluded from analysis due to lack of data on liver volume at the end of the study. The Committee was informed that patients treated with octreotide LAR in the first phase of the study did not see any significant change in liver volume during the open-phase. Patients that had been treated with placebo during the double-blind phase saw a significant reduction in liver volume when they entered the open-phase receiving octreotide LAR (5360 ± 3331 mL reduced to 4952 ± 3344 mL, p=0.01). Kidney volume, which had reduced during the first year on active treatment, started to increase during the second year; renal function continued to decline whilst patients were on octreotide LAR.

The Committee questioned the main aim of treatment with octreotide in PLD, being symptomatic relief, and in severe cases to avoid resection or transplantation, as it was felt that successful treatment should be able to demonstrate a reduction in mortality [no data presented]. The Committee further questioned whether this intervention would be considered more cost-effective than surgery; however, again there were no data presented to answer this question. The Committee was advised from the application that the annual cost of treatment for one patient with octreotide LAR is approximately £20,000 per annum. The Committee were uncertain if NHS England would fund this treatment, as part of specialised commissioning, if approved, based on the data available.

Dr Gale explained that there are currently three or four patients at Royal Free Hospital who are on the transplant list, but may benefit from this treatment. This condition usually presents in adults in their 30's, particularly young women of child bearing age.

The Committee asked Dr Gale if he would consider treatment with octreotide short-acting injection on the basis of it being significantly cheaper. Dr Gale explained that there is no evidence that short-acting octreotide would be beneficial in this patient group, and also that it requires thrice-daily administration compared with once-monthly injection therefore having a significant impact on patients' lives as they would need to inject themselves more frequently. Dr Gale however clarified that in practice, patients at RFH would initially be trialled on the short-acting formulation for one month with those showing a treatment response being converted to the long-acting formulation.

In light of the lack of compelling evidence from the RCTs and extension study (reporting on one year of treatment), the Committee asked Dr Gale whether he thought the effects were sustained into the second year. Dr Gale explained that in his experience, patients do respond, but there is no cure; any reduction in volume of liver will be sustained with no further reduction. Although the treatment effect was unlikely to be pronounced in year two, the Committee agree that it would be difficult to withdraw treatment from patients after one year.

In summary, due to concerns related to price and optimal duration of therapy for symptomatic management ahead of transplantation, the Committee agreed that octreotide long-acting injection should not be added to the NCL Formulary for the above indication.

7. Guideline: Treatment for Over Active Bladder (OAB) Syndrome

Mr Bodalia presented an updated guideline for the management OAB syndrome. This update follows on from a previous Committee review which generated comments as well as comments received from various Consultants (Urology, Gynaecology and Care of the Elderly) as part of a wider consultation.

Mr Bodalia informed the Committee that in addition to the above, the revised document incorporates the recommendations from NICE CG 171, NICE TA 290 and an updated (in-house) network meta-analysis, the result of which has changed the ordering of the drugs from the previous guideline. Although solifenacin and modified-release oxybutynin were found to be the most effective treatments, the Committee noted that the difference in micturition frequency between all treatments included within the analysis was small and probably clinically insignificant. It was noted that this guideline would have a significant financial impact for CCGs if these two recommended treatments are prescribed in place of the current choices. The CCG representative informed the Committee that they, in accordance with their current local guideline, have worked hard to switch prescribing away from solifenacin with one CCG reporting annual savings of £60k per annum. Ms N Shah shared with the Committee the findings of a recently conducted GP-level audit within Camden CCG which reported that patients could be effectively initiated on oxybutynin immediate-release first line.

The Committee agreed that it is important to establish which drugs are preferred for OAB as there have been challenges getting everyone to agree to cost effective prescribing options, with a preference towards the first-line options being agents which are off-patent. The CCG representatives noted that there has been a significant increase in the use of mirabegron under the recommendation of Consultant Urologists; however, this is likely to have been in accordance with the criteria specified within NICE TA 290.

Based on the concerns raised, the Committee did not approve this guideline and agreed that the recommendations needed to be revisited in the context of benefit vs. cost for all treatments included

within the analysis. The Committee however agreed that there is a need for a joint treatment pathway to be developed between primary and secondary care.
Action: Mr Bodalia to revise the guideline; Mr Minshull to co-ordinate the update with the CGG representatives

8. Pathway: Rheumatoid Arthritis

Mr Thakrar presented a one-page flow-diagram pathway for the treatment of rheumatoid arthritis (RA). The JFC welcomed Dr Leandro and Dr Manson (Consultant Rheumatologists, UCLH) who attended to assist with any point requiring clarification.

Mr Thakrar informed the Committee that approximately 18 months ago applications for rituximab, abatacept and tocilizumab for use as monotherapy in RA (i.e. without co-prescription of a DMARD and therefore outside of NICE guidance) were approved. The aim of this pathway was to clarify when each of the approved treatments would be used in accordance with the current NICE approved treatment pathway. Dr Leandro and Dr Manson clarified that this pathway has been discussed with Consultant Rheumatologists at Royal Free and Whittington Health. Mr A Shah and Ms H Mehta requested that a copy be sent to the RNOH and NMH Rheumatologists for comments

The pathway specified abatacept and tocilizumab as first-line treatments when monotherapy is indicated (in addition to NICE approved adalimumab, etanercept, and certolizumab), with rituximab reserved as a second-line treatment option. The Committee was advised that although NICE guidance will be considered for all patients, patients with a seronegative status are less likely to respond to rituximab. The Committee questioned the role of infliximab in RA, particular as it now available as a more cost-effective biosimilar preparation. Dr Manson explained that there is a patient preference towards the subcutaneous preparations as they are more convenient and cause less disruptions to life style, with infliximab generally reserved for a small group of patients with a mixed clinical picture.

The Committee were concerned that the pathway circulated differed somewhat from the current NICE pathway, however Mr Thakrar explained that there has been a lot of new data since NICE published their pathway and there is a delay in publication of the update owing to a number of developments within this area including the launch of a number of biosimilars. In addition, the Committee were informed that many other trusts have implemented a similar pathway already.

The Committee ratified this pathway subject to the correction of formatting issues being rectified and appropriate Rheumatologists being informed. CCGs agree to support treatment in line with the pathway. Once the updates have been completed all three treatments will be available for prescribing in accordance with the pathway.
Action: Dr Leandro and Dr Manson to make the suggested amendments and ensure that Rheumatologist from each of the Acute Trusts within NCL (where relevant) have agreed to the pathway. The final pathway is to be forwarded to Mr Bodalia

9. Local DTC recommendations / minutes

NMUH

- **Endoclot** Is a haemostatic device sprayed on to bleeding site in upper-GI, non-variceal bleeding. It has been proposed as last-line (3rd line) option where standard therapies have failed. Endoclot devices are supplied through pharmacy an NMUH. The Committee agreed that a pathway should be created across NCL to standardise the place in therapy.

10. Next meeting

Thursday 30th July, Room 6LM1, Stephenson House, 75 Hampstead Rd.

11. Any Other Business

Nil