North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 18th February 2021

Present:	Prof R Sofat	NCL JFC Chair	(Chair)
	Dr A Sell	RNOH, DTC Chair	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr P Gouldstone	NCL CCG, Head of Medicines Management (Enfield)	
	Mr G Kitson	WH, Deputy Chief Pharmacist	
	Ms G Smith	RFL, DTC Chair	
	Mr A Dutt	NCL CCG, Head of Medicines Management (Islington)	
	Mr T Dean	Patient Partner	
	Dr K Tasopoulos	NMUH, DTC Chair	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms P Taylor	NCL CCG, Head of Medicines Management (Haringey)	
	Mr S Semple	MEH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Ms S Lever	NCL CCG, Head of Medicines Management (Barnet)	
	Dr D Burrage	WH, Consultant in Emergency Medicine	
	Dr S Ishaq	WH, Consultant Anaesthetist	
In attendance:	Dr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Barron	North London Partners, MEP Project Lead	
	Mr G Grewal	North London Partners, JFC Support Pharmacist	
	Ms M Kassam	North London Partners, JFC Support Pharmacist	
	Mr H Weaver	NHSE, Specialised Commissioning Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor High Cost Drugs	
	Ms SY Tan	NEL CSU, Contracting and Commissioning Pharmacist	
	Ms A Tynan	RFL, Medicine specialities pharmacist	
	Mr D Abdulla	RFL, Clinical Pharmacist	
	Ms L McLaughlin	NCL Head of Cancer Commissioning	
	Dr M Cohen	RFL, Consultant in Endocrinology and Diabetes	
	Dr A Lamba	Lead clinician for Barnet Federated GPs Diabetes Network	
	Dr D Patel	RFL, Consultant in Endocrinology and Diabetes	
	Ms D Hicks	Medicus Health Partners, Diabetes Nurse Consultant	
	Dr P Harrow	UCLH, Consultant Gastroenterologist	
Apologies:	Mr S Richardson	WH, Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Dr M Kelsey	WH, DTC Chair	
	Mr A Tufail	MEH, DTC Chair	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Ms S Stern	NMUH, Chief Pharmacist	

2. Meeting observers

Ms Weaver (NHSE, Specialised Commissioning Pharmacist) was welcomed as an observer of the meeting.

3. Minutes of the last meeting

The minutes and abbreviated minutes of the 19 November 2020 and 8 December 2020 meeting were accepted as accurate reflections of the meetings.

4. Matters arising

4.1 Oxford-AstraZeneca vaccine for COVID-19

The Committee was informed that the Oxford-AstraZeneca vaccine for COVID-19 was approved via Chair's action in January 2021.

4.2 Tocilizumab and sarilumab for patients with COVID-19

In December 2020, JFC Support wrote to DTCs encouraging continued enrolment into trials rather than off-label use of tocilizumab – a sentiment which was supported by a joint statement from the 'Faculty of Intensive Care Medicine' and the 'Intensive Care Society', and 'COVID-19 Therapeutics Support and advice Group' (CTAG).

Since then, REMAP-CAP and RECOVERY have both published favourable results for IL-6 use in severe disease and NHSE/I have issued multiple Interim Clinical Commissioning Policies which were reviewed and approved via Chair's Action:

- Sarilumab for critically ill patients with COVID-19 pneumonia (adults) - 17 February 2021
- Tocilizumab for critically ill patients with COVID-19 pneumonia (adults) - 17 February 2021

The current interim clinical commissioning policy advises to use sarilumab in the REMAP-CAP cohort where possible to reserve supply of tocilizumab for the RECOVERY cohort. It was agreed that individual Trusts need to consider the risks and benefits of this approach. The benefit is to preserve tocilizumab stocks. The risks involve using two drugs for similar indications in a single clinical area which have different approval requirements (sarilumab requires two-consultant sign-off), exclusion criteria and administration requirements (sarilumab requires a 0.2-micron filter in the infusion line).

4.3 Cannabis-based medicinal products: minor update

This item was deferred from the previous meeting. Information and relevant updates were circulated to the membership with overall agreement to approve. The final documents were included for reference.

4.4 Position Statement: Etoricoxib for rheumatological indications

At the December JFC meeting, etoricoxib for rheumatological indications was approved subject to a position statement being developed to support safe prescribing practice. The position statement provides inclusion and exclusion criteria and appropriate dosing. The Committee approved the statement and etoricoxib was added to the NCL Joint Formulary as per the conditions of the position statement.

5. JFC Outstanding Items & Work Plan

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

6. Members declarations of conflicts of interest

Nil

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
MEH	Jan + July 2020	Intravitreal triamcinolone	Treatment of cystoid macular oedema secondary to non-infectious uveitis in the posterior segment of the eye, not otherwise appropriate for Ozurdex® (dexamethasone intravitreal implant) or Iluvien® (fluocinolone acetonide intravitreal implant)	Decision: MEH only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

MEH	Jan + July 2020	Intravitreal triamcinolone	Prevention of cystoid macular oedema secondary to non-infectious, inactive, uveitis in the posterior segment of the eye, for patients unable to use high-dose corticosteroids	Decision: MEH only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
MEH	July 2020	Insulin eye drops	Persistent epithelial defects when conventional treatment have failed	Decision: MEH only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
MEH	July 2020	Bevacizumab intravitreal injection	Early treatment of wet AMD as part of the NCL pathway update	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Approved clinically, Funding TBC Fact sheet or shared care required: No
RFL	Nov 2020	Human fibrinogen (Tisseel)	Pterygium excision surgery	Decision: Added to the NCL joint formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
RFL	Nov 2020	Besilesomab	Scintigraphic imaging in suspected osteomyelitis	Decision: RFL only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
RFL	Nov 2020	JAK inhibitors (Baricitinib, Ruxolitinib, Tofacitinib)	STAT GOF mutations in Primary Immunodeficiency	Decision: RFL only Prescribing: Secondary care Tariff status: Excluded from tariff, not routinely commissioned Funding: Trust Fact sheet or shared care required: No Additional information: Pathway in development. Tofacitinib would be the preferred choice (unless contraindicated).
RFL	Dec 2020	IV Ferric carboxymaltose (Ferinject®)	Iron deficiency anaemia associated with inflammatory bowel disease in paediatrics >8yrs where oral therapy not appropriate	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
UCLH	Nov 2020	Cefixime	Second line prophylaxis to prevent irinotecan-associated diarrhoea in children and adolescent oncology patients	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

UCLH	Nov 2020	Osimertinib	Leptomeningeal metastases in EGFR-mutated Non-Small Cell Lung Cancer (irrespective of previous tyrosine kinase inhibitor treatment or T790M status)	Decision: Added to the NCL joint formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No Additional information: Licensed 80mg daily dose

7.2 Not approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Nov 2020	Regorafenib	FoC: Second line treatment of metastatic cholangiocarcinoma following progression with gemcitabine and a platinum-based therapy	Decision: Not approved
UCLH	Nov 2020	Osimertinib 160mg daily dose (off-label)	Leptomeningeal metastases in EGFR-mutated Non-Small Cell Lung Cancer (irrespective of previous tyrosine kinase inhibitor treatment or T790M status)	Decision: No approved

8. New Medicine Reviews

8.1 Switching GnRH analogues in prostate cancer patients to triptorelin

The Committee considered a proposal to switch 3-monthly leuprorelin or 3-monthly goserelin to 3-monthly triptorelin with eventual progression to the 6-monthly formulation for patients with prostate cancer. This proposal follows an STP wide workstream to support patients with prostate cancer to receive treatment in primary care. All agents are known to be effective for this indication, the consideration here was to reduce the number of interactions that patients would require to receive this treatment (an advantage during the pandemic), the switch would benefit overall cost and standardise practice across the sector whilst maintaining clinical efficacy.

Evidence reviewed was limited to switching rather than efficacy for the underlying indication which is well documented. Cornford et al. was a multi-centre, retrospective study to assess the impact on patient-healthcare interactions and efficacy of switching to a 6-monthly triptorelin preparation. 88 patients who had two years of retrospective notes were included in the study, of which 41 patients were switched from previously being on a 3-monthly preparation of goserelin (n=28) or a 3-monthly preparation of triptorelin (n=13). The primary endpoint, reduction in patient-healthcare interactions, was significantly reduced when switched to 6-monthly triptorelin compared with baseline (reduction by 41.5% overall [p<0.0001]). Median serum PSA levels from evaluable patients (n=36) were 0.35ng/mL at baseline; at 6 months, PSA was 0.18ng/mL, and at 12 months, PSA was 0.24ng/mL, demonstrating maintenance of PSA control. Key limitations of the study were the retrospective, non-randomised design, the small patient numbers, and no detail of testosterone level following the switch. The switch made in this study was from a 3-monthly GnRH analogue to a 6-monthly triptorelin formulation, whereas the STP pathway suggests switching between 3-monthly formulations.

In terms of safety, the risk of using any GnRH analogue is low, though there are slight differences between formulations. The 6-monthly formulation can only be administered via intramuscular injection and therefore unsuitable for patients on anticoagulation. Monitoring following initiation includes serum PSA (to monitor disease progression) and testosterone levels (to confirm castrate testosterone levels). There is insufficient data and lack of consensus on the appropriate monitoring frequency post-switch. regions. It has been suggested by the stakeholder group that PSA and testosterone could be measured at the time that coincides with the next dose.

In terms of budget impact, the switch is expected to be cost-neutral initially but may become cost-saving in the long-term due to the reduction in injection frequency associated with the 6-montly formulation.

In terms of convenience, triptorelin administration may be more comfortable and the move to administer doses in the community is preferred by patients. The 6-monthly administration option would also reduce the number of appointments needed.

The Committee heard from Ms McLaughlin (NCL Head of Cancer Commissioning) that patients would be consented to switching formulations, and 80% are anticipated to switch to triptorelin, and 50% of these patients will eventually progress to the six-monthly formulation. The use of the six-monthly preparation will help resource and capacity, and will allow for a robust training programme for the primary care workforce. Moreover, during the preparation for this application the stakeholder group had also included patient partners and were supportive of this switch.

In camera, the Committee recognised that all GnRH analogues are licensed to treat this patient cohort, with castrate testosterone levels detected after 28 days. It was also recognised that there are no side-by-side comparisons of products available. The Committee was satisfied that a switch would be clinically appropriate, though could not comment on an appropriate monitoring regime as guidance for this amongst specialists in the UK appears to be varied.

In summary, the Committee agreed that a switch between 3-monthly formulations of GnRH analogues would be clinically appropriate and can be conducted in primary care with specialist advice. The monitoring regime would need to be decided by NCL specialists and an NCL Fact Sheet will be produced to support primary care practitioners.

Decision: Approved
Prescribing: Primary and Secondary care
Tariff status: In tariff
Funding: Hospital and CCG
Primary and secondary care Fact sheet or shared care required: Yes

8.2 Dulaglutide higher doses (Trulicity®) for type 2 diabetes (Applicant: Dr Cohen, RFL)

The Committee considered a request for higher dose dulaglutide (3.0 mg and 4.5 mg), a GLP-1 receptor agonist, for patients with type 2 diabetes who meet NCL criteria for GLP-1 receptor agonist initiation. Standard dose dulaglutide (1.5 mg and 0.75 mg) is already on the NCL Joint Formulary.

AWARD 11 was a 52-week, Phase IIIb, active-comparator controlled study to compare the efficacy and safety of higher doses of dulaglutide to dulaglutide 1.5 mg for patients with type 2 diabetes on stable dose of metformin and HbA1c 7.5% to 11% (n= 1,842). Patients were randomised 1:1:1 to 1.5 mg, 3.0 mg or 4.5 mg once-weekly. The primary endpoint, HbA1c reduction at week 36, was superior with dulaglutide 4.5 mg compared to dulaglutide 1.5 mg (estimated treatment difference -0.24% (95% CI: -0.36 to -0.11%). For the comparison of dulaglutide 3.0 mg and dulaglutide 1.5 mg, an improvement in HbA1c was seen in some, but not all, analyses. Weight loss was superior with the higher doses of dulaglutide.

In terms of safety, serious adverse effects were not higher with the higher doses. Prevalence of gastrointestinal adverse effects were somewhat higher however the EMA did not consider this an important issue since dose reduction would be possible if higher doses were not tolerated.

In terms of budget impact, higher dose dulaglutide is expected to be cost-neutral.

Dr Cohen (RFL), Dr Lamba (Barnet), Dr Patel (RFL) and Ms Hicks (Medicus Health) declared conflicts relevant to dulaglutide and most other branded medicines used in diabetes. The Committee heard that higher doses would be offered to patients on treatment with dulaglutide 1.5 mg whose HbA1c is above their target, as an alternative to switching to semaglutide subcutaneous or initiating insulin.

In camera, the Committee agreed that small but relevant reductions in HbA1c (~0.2%) and body weight (~1Kg) were observed with the higher doses than with dulaglutide 1.5 mg. The positioning of dulaglutide relative to subcutaneous semaglutide was not considered, any request to use it as a first-line option (e.g. in patients without cardiovascular disease) should first be agreed at NCL Diabetes Transformation Board before bringing back to NCL JFC for consideration.

In summary, the Committee agreed to add higher dose dulaglutide to the NCL Joint Formulary for patients who are on treatment with dulaglutide 1.5 mg and whose HbA1c is above their target. Dulaglutide at the current time remains second-line to *subcutaneous* semaglutide and is restricted for patients who are needle phobic, have impaired manual dexterity and who require administration by a

third-party (to reduce the risk of needlestick injury) although an application is welcomed to review this positioning.

Decision: Approved
Prescribing: Specialist initiation, continuation in primary care
Tariff status: In tariff
Funding: Trusts and GPs
Primary and secondary care Fact sheet or shared care required: The need for a GP Fact Sheet will be reviewed following conclusion of the NCL Diabetes Pathway work.

8.3 Oral Semaglutide (Rybelsus®) for type 2 diabetes (Applicant: Dr Cohen, RFL)

The Committee considered an application for *oral* semaglutide, a GLP-1 receptor agonist, for patients with type 2 diabetes who meet NCL criteria for GLP-1 receptor agonist initiation. The application requested restricted approval to (i) those who are unable to use injectable GLP-1 receptor agonists and (ii) to facilitate optimisation of diabetes control for patients reviewed via non-face-to-face consultations. *Subcutaneous* semaglutide is already on the NCL Joint Formulary.

PIONEER 4 was a, 52-week, Phase III, placebo and active comparator controlled study to compare the efficacy and safety of *oral* semaglutide to placebo and liraglutide 1.8 mg for patients with type 2 diabetes taking metformin +/- SGLT2i with HbA1c 7.0% to 9.5% (n=711). Hierarchical statistical testing was undertaken for (i) change in HbA1c superiority vs. placebo, (ii) change in HbA1c non-inferiority vs. liraglutide and (iii) change in body weight superiority compared to both liraglutide and placebo at week 26. *Oral* semaglutide provided superior glycaemic control compared to placebo (estimated treatment difference -1.1% [95% CI: –1.2 to –0.9%]), non-inferior glycaemic control to liraglutide 1.8 mg (estimated treatment difference –0.1% [95% CI: –0.3 to 0.0%]) and superior weight loss compared to both placebo and liraglutide 1.8 mg. Key limitations of the study were place in therapy (75% 2nd line; which does not match use in NCL) and the wrong active comparator (*subcutaneous* semaglutide or dulaglutide are preferred).

A meta-analysis found *oral* semaglutide is likely to be ranked lower than *subcutaneous* semaglutide in terms of HbA1c and weight reduction, although the differences were small (~0.2% and 0.6 Kg) and not statistically significant. *Oral* semaglutide is expected to be similar to dulaglutide 4.5 mg in terms of HbA1c but better in terms of weight reduction.

PIONEER 6 was a, cardiovascular safety study comparing *oral* semaglutide to placebo, both in addition to standard-of-care for patients with type 2 diabetes at high cardiovascular risk. The primary outcome was major adverse cardiovascular event (composite of CV death, non-fatal MI, non-fatal stroke). The study was 'event driven' meaning it terminated when a predetermined number of events had occurred, and was designed to test (i) non-inferiority to placebo and (ii) superiority to placebo. The study found *oral* semaglutide was non-inferior but not superior to placebo. Key limitations of the study were the short study duration, the fact that all patients took max licensed dose (unlikely to occur in clinical practice) and the high baseline CV risk profile limiting generalisability to all patient eligible for GLP-1 receptor agonist use in NCL.

In terms of safety, *oral* semaglutide was associated with a low risk of serious adverse effects, similar to other GLP-1 receptor agonists already on formulary.

In terms of convenience, *oral* semaglutide needs to be taken in the morning in a fasted state, with up to half a glass of water, and wait 30 min or longer before their first meal, any other drinks, and taking any other oral medication. This necessitates an additional dosing time point and will increase dosing frequency to three times per day for most patients (on waking, with breakfast and evening). It is known that increasing dosing frequency is correlated with reduced compliance, and furthermore, reduced compliance is correlated with impaired glycaemic control. Reduce compliance may be of particular concern with this drug as non-compliance has a significant impact on absorption and therefore effectiveness.

In terms of budget impact, *oral* semaglutide has the same annual treatment cost as other GLP-1 receptor agonists. It is feasible that adding an oral option to formulary would bring GLP-1 receptor agonist initiation earlier in the treatment pathway which would be associate with a considerable budget impact.

Dr Cohen (RFL), Dr Lamba (Barnet), Dr Patel (RFL) and Ms Hicks (Medicus Health) declared conflicts relevant to *oral* semaglutide and most other branded medicines used in diabetes. The Committee heard that whilst *oral* semaglutide had not demonstrated cardiovascular benefit, this was expected because the drug is the same as for *subcutaneous* semaglutide and an additional CVOT study (SOUL) is ongoing to prove this. The Committee heard that some patients will not accept injectable medicines, including dulaglutide which does not have a visible needle, and this is seen more commonly in the BAME community. However, no evidence of this was presented and the committee questioned if there were data to support this or if this may be confounded by a number of health as well as a number of other factors. Moreover the committee was not clear if compliance to an oral medicine (particularly with increasing the dosing frequency) would be better. This may be a particularly important consideration in those with diabetes who have multiple co-morbidities and therefore often on a number of medicines as well. The committee agreed the oral formulation is easier to initiate in virtual clinics.

In camera, the Committee agreed that there was a place in therapy for an oral medicine which effectively lowers HbA1c and body weight. However, the Committee were not assured that *oral* semaglutide would inevitably improve cardiovascular outcomes due to (i) known large variability in drug exposure following administration for which non-compliance is likely to play a role, (ii) PIONEER 6 did not demonstrate superiority, (iii) PIONEER 6 titrated all patients to 14 mg which is unlikely to reflect real-world use and (iv) there is equipoise because a subsequent study was considered ethically acceptable. The EMA agree with this view and rejected Novo Nordisk's attempt to pool cardiovascular safety data for both oral (14 mg) and subcutaneous (0.5mg and 1mg) forms. The Committee expressed concern that adding an oral option could lead to prescribing creep and safeguards were required. It was unclear whether 'ease of prescribing in virtual clinic' was a sufficient reason to initiate a medicine without proven benefit in cardiovascular outcomes.

In summary, the Committee agreed there was a place for oral semaglutide on the NCL Joint Formulary however deferred to the NCL Diabetes Transformation Board to agree restrictions on use which should reflects the following:

- GLP-1 receptor agonists to be initiated by diabetes specialists
- *Subcutaneous* semaglutide and dulaglutide are preferred as they have demonstrated cardiovascular benefit
- *Oral* semaglutide should only be offered where the patient has confirmed they can comply with the fasting administration requirement (including no tea, coffee, milk, food, other medicines for 30 minutes after dosing) and an increase in total daily dosing frequency.

Decision: Deferred

8.4 Anti-TNF dose intensification in primary non-response for Ulcerative Colitis and Crohn's Disease (Applicant: Dr Harrow, UCLH)

The Committee considered an application for dose intensified adalimumab (40mg weekly) or infliximab (10mg/kg 8 weekly or 5mg/kg 4 weekly IV), for patients with ulcerative colitis (UC) or Crohn's disease (CD) who experience a 'primary non-response', defined as an inadequate response to the first 12 weeks of standard dose anti-TNF. The existing NCL pathways currently require primary non-responders to be switched to an alternative biologic. The applicant proposes that, where available, patients undergo therapeutic drug monitoring (TDM) and only those with low serum drug levels are offered dose escalation.

There are no RCTs investigating the effectiveness of anti-TNF dose intensification for primary non-response. High quality observational data is also lacking. However the data that were available that may aid the committee informing any decisions was heard.

Karmiris *et al* was a single centre observational study of adalimumab in UC. The study was designed to identify the number of patients who responded to treatment by week 4 & 12, and of those, the proportion who demonstrated a sustained clinical benefit (n=168). At week 4, 7% discontinued therapy, mostly due to primary non-response, however 24% continued despite an unsatisfactory response. In this subgroup, 80% (n=32) were escalated to adalimumab 40mg weekly and 62.5% (20/32) responded. Response was defined as an improvement in symptoms according to clinician judgement. It is not known what proportion of patients would have responded had standard dosing been maintained.

It is well documented that low serum drug concentrations are associated with a higher likelihood of treatment failure. For example, the 54-week, UK-wide, multicentre, prospective, observational study reported by Kennedy *et al* found that among patients who continued treatment beyond week 14, drug concentrations at week 14 was independently associated with non-remission at week 54.

In terms of safety, the recent CALM study, which randomised people to 'tight clinical control' or 'usual clinical management', with the former being more likely to receive dose-escalated adalimumab, found adverse events rates were similar in both arms. Further, dose escalated infliximab and adalimumab is already routinely used for secondary non-response in UC and CD.

In terms of budget impact, anti-TNF dose intensification is expected to cost up to £58,000 in Year 1 depending on the duration of dose intensification however much, if not all, of this is expected to be offset by delaying the use of more expensive medicines (e.g. vedolizumab, ustekinumab or tofacitinib)

The Committee heard from Dr Harrow that the purpose of the application is to resolve current inequity of access across NCL, as currently dose escalation for primary non-response is standard practice in UCLH only. UC and CD are long-term conditions with a limited number of therapeutic agents therefore the ability to dose-escalated for primary non-response is clinically desirable to ensure patients are retained on their first-line biologic for as long as possible.

In camera, the Committee agreed the quality of evidence to support anti-TNF dose intensification for primary non-response was extremely low, however agreed it was reasonable to expect that patients with low drug levels may respond to dose intensification. It was acknowledged that NCL IBD clinical leads were rapid adopters of best value biologics therefore the 'cost per dose' was low and subsequently infliximab and adalimumab were cost-effective treatments at both standard and dose-escalated doses.

In summary, the Committee approved infliximab and adalimumab dose intensification for patients with UC or CD who experience a primary non-response to standard dose anti-TNF.

Decision: Added to the NCL Joint Formulary
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: CCG
Primary and secondary care Fact sheet or shared care required: No

8.5 Anti-TNF continuous dose intensification for secondary loss of response in Ulcerative Colitis and Crohn's Disease (Applicant: Dr Harrow, UCLH)

The Committee considered an application for continuous dose intensified adalimumab (40mg weekly) or infliximab (10mg/kg 8 weekly or 5mg/kg 4 weekly IV), for patients with ulcerative colitis (UC) or Crohn's disease (CD) who experience a secondary loss-of-response to standard dose anti-TNF. The existing UC & CD pathways allow for dose escalation however require that all patients deescalate treatment after 16 weeks. The application is to remove the 16-week de-escalation requirement thereby allowing patients with poor prognostic factors, who respond to escalated doses, to continue treatment until it is clinically appropriate to dose reduce. The applicant proposes that, where available, patients experiencing secondary loss-of-response undergo therapeutic drug monitoring (TDM) and only those with low serum drug levels and low anti-drug antibody levels are offered dose escalation.

Dose intensified adalimumab is licensed for UC and CD whereas dose intensified infliximab is licensed for CD only. NICE TA187 and TA329 recommend both drugs, within their licensed indications, for CD and UC. Neither TA recommend that dose-escalation should be restricted to blocks of 16-weeks. In January 2018, JFC approved dose intensified infliximab for secondary loss-of-response in UC but did not recommend a specific duration. The British Society of Gastroenterology support the use of dose intensification, and subsequent de-escalation, however do not specify that this should be done within a specific time interval.

There are no RCTs comparing 'fixed duration' and 'clinically guided duration' anti-TNF dose intensification in patients with secondary loss-of-response. Evidence that could inform the committees decision was heard.

The Committee first reviewed the evidence relating to fixed duration anti-TNF dose intensification. An LMEN review from 2015 concluded "little guidance or reliable evidence on when and how to de-escalate doses of adalimumab or infliximab safely and successfully". The largest study identified included 720

patients who received dose escalated adalimumab; de-escalation was attempted in 54% of patients after a median duration of 3 months and was successful in 63% of these patients. The fixed duration anti-TNF dose intensification is therefore not supported by a strong evidence-base.

Clinical practice in NCL is to use therapeutic drug monitoring (TDM) to guide treatment for patients who experience treatment failure (either primary failure or secondary loss-of-response); patients with low drug levels will be considered for dose-escalation and those with therapeutic levels will be switched. This differs from prospective TDM (i.e. dose adjustment based on drug levels rather than clinical response) which was investigated in TAXIT and NOR-DRUM-A (both negative) and is being investigated in NOR-DRUM-B.

Eight observational studies were identified which report rates of remission/response following dose escalation in patients who experience secondary loss-of-response; remission rates ranged from 19% to 94.1%. The wide range is due to variation in dosing, definitions for remission/response and combination therapy with concurrent corticosteroids or immunosuppressives. Additionally, clinical decision making about dose escalation, de-escalation or discontinuation of medication within the studies may have also been subject to variability; some studies lacked use of objective tests and/or validated and standardised measure of disease activity and some studies allowed for second dose intensification. For the most part, these results were short-term, with only a couple of studies reporting results for more than 2 years and limited by the sample size (mostly n<100).

In terms of budget impact, the proposal is estimated to cost an additional £130,000 per annum across NCL.

The Committee heard from Dr Harrow that the requirement to deescalate treatment after 16 weeks is not an evidence-based strategy and increases the risk of a patient relapsing. Since the decision was taken to de-escalate treatment after 16 weeks, the cost of infliximab and adalimumab has lowered substantially. Dose intensification may delay progression to alternative agents which are more expensive.

In camera, the Committee agree the requirement to deescalate treatment after 16 weeks as it was not supported by a strong evidence-base. In November 2020, the Committee rejected a proposal to use 1st line vedolizumab for UC, in part because the study did not permit the use of dose-escalate adalimumab in the comparator arm, therefore it would be inconsistent to reject the current proposal. It was acknowledged that NCL IBD clinical leads were rapid adopters of best value biologics therefore the 'cost per dose' was low and therefore infliximab and adalimumab were cost-effective at both standard and dose-escalated doses.

In summary, the Committee agreed that patients who experience a secondary loss-of-response to standard dose anti-TNF could receive dose-escalated therapy until a clinical decision to de-escalate treatment during regular 6-12 month reviews.

Decision: Added to the NCL Joint Formulary
Prescribing: Secondary care
Tariff status: Excluded from tariff
Funding: CCG
Primary and secondary care Fact sheet or shared care required: No

9. Uterotonic pathway in patients undergoing Caesarean section

In November 2020, the Committee deferred approval of the uterotonic pathway to address outstanding concerns, including how women who switch from vaginal to Caesarean delivery are treated, aligning the pathway with new guidance from NMUH, and understanding the use of oxytocin doses and administration methods from the Cochrane review discussed in the JFC evaluation. A working group was established which included representation from all Trusts. The scope of the pathway was amended to include patients entering from the vaginal delivery pathway, and the order of uterotonics was agreed. The pathway recognised that some patient populations may not be suitable for all treatments. Concerns raised regarding oxytocin regimens being compared to carbetocin were allayed. The Committee was supportive of the revised pathway, and NCL Trusts were asked to adopt the pathway within local guidance.

The Committee agreed to add carbetocin for the prevention of postpartum haemorrhage in women undergoing Caesarean section, pending local adoption of the NCL agreed uterotonic pathway and local financial consideration.

Decision: Approved (subject to local Trust adoption of the NCL uterotonic pathway and local financial consideration)
Prescribing: Secondary care only
Tariff status: In tariff
Funding: Hospital
Primary and secondary care Fact sheet or shared care required: N/A

10. Dexamethasone on discharge in COVID-19 patients

The Committee was informed that NICE now recommend dexamethasone is continued for 10 days or until discharge, and that being on a 'virtual ward' is not classed as discharged.

11. AOB

11.1 Oral aminophylline (Phyllocontin®) discontinuation

The Committee were informed that oral aminophylline modified release tablets (Phyllocontin®) were being discontinued, with supply exhaustion expected at the end of March. The Committee agreed that Phyllocontin® should be removed from the NCL Joint Formulary, and no new initiations should take place. For patient who require an oral methylxanthine to be continued, theophylline modified release tablets is a suitable alternative.

Decision: Removed from the NCL Joint Formulary

12. Next meeting

Thursday March 18th 2021