NHS GRAMPIAN
Minute of Formulary Group Meeting
Tuesday 20 August 2019 at 14:30 in the Seminar Room, David Anderson Building

PRESENT	**APOLOGIES**	**APPROVED**
Ms A Davie	Dr D Culligan	
Ms F Doney	Dr A MacDonald	
Dr L Elliot	Dr A Sun	
Dr J Fitton		
Ms M Galvin (from item 4.1)		
Mrs L Harper		
Professor J McLay (Chairman)		
Mrs L Montgomery		
Dr W Moore		
Mr M Paterson		
Mr C Rore		
Mr R Sivewright		

IN ATTENDANCE
Dr Prakash Abraham, Consultant Endocrinology and Diabetes, Clinical Lead Endocrinology, for item 4.2.
Ms Caitlin Wilkinson, Formulary Team administrator.

Note some items were taken outwith the agenda running order.

ITEM	**SUBJECT**	**ACTION**
	The Chairman welcomed members, opened the meeting and noted that a quorum was present.	
1.	**APOLOGIES**	
	Apologies for absence were requested and noted.	
2.	**DRAFT MINUTE OF THE MEETING HELD 16 JULY 2019**	
	The Group accepted the draft note of the meeting subject to minor typographical changes.	**FD**
	The corrected final approved minute will be in the public domain within 21 days of approval.	**FD**
3.	**PRESENTATION – NONE**	
4.	**MATTERS ARISING**	
	4.1. ACTION LOG	
	Noted.	
6.	**6.1. FG1 415/18 TOLVAPTAN (SAMSCA®) (HYPONATRAEMIA SECONDARY TO THE SIADH)**	
	The Chairman welcomed Dr Prakash Abraham, Consultant Endocrinology and Diabetes, to the meeting. Dr Abraham attended the meeting to discuss the request to review the formulary classification of tolvaptan, as the brand Samsca®, to allow prescribing in Primary Care. At the June meeting, the Group accepted the restricted local need for Samsca® for use in a limited group of adults with severe hyponatraemia that is refractory to standard treatment options. To minimise the potential for inappropriate widespread use, prescribing was restricted by indication and clinician - *should only be prescribed on the recommendation of a consultant endocrinologist. Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, treatment with Samsca® has to be initiated in hospital. The classification given was 1b - available for restricted use under specialist supervision and 8b – recommended for hospital use only*. Ms Doney tabled updated draft departmental guidance for tolvaptan. The revised version included a scenario where patients were not followed up by the Oncology or Neurorehab services.	

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Dr Abraham discussed the experience from recent cases where Samsca® was used to normalise patients' sodium levels but ongoing prescribing in Primary Care was requested.

Dr Abraham confirmed that:
- the service has limited experience of the use of Samsca®
- the Endocrine Service can provide Primary Consultants or General Practitioners directive advice in terms of frequency of monitoring and dosing. However, the Endocrine Service does not directly manage these patients, i.e. does not follow-up/see patients at Endocrine clinics, and may never actually see these patients.
- the Endocrine Service is being asked for advice regarding the management of patients and it is problematic/impractical for the Service to manage the logistics of Samsca® prescribing (prescriptions written, medication dispensed and supplied)

The Chairman thanked Dr Abraham for attending the meeting, and Dr Abraham left the meeting before decision-making.

The Group noted:
- tolvaptan, as the brand Jinarc®, is included on the formulary for use in polycystic kidney disease (PKD), is also classified 'Hospital only' and prescribing is managed by the Renal Physicians. People with PKD kidney disease are generally stable and the Renal Physicians take responsibility for these patients.
- the case presented in June described short-term use, with the rare exception of a longer treatment duration when used in a palliative setting. The expectation was that by treatment of the underlying disease the patient's hyponatraemia would resolve and ongoing treatment was not required.
- the practicalities/logistics of supply are outwith the remit of the Group, as is approval of the departmental guidance
- General Practitioners are not acquainted with Samsca® as a medicine, and they have no experience of its use
- the risk of an adverse event is higher if Primary Care clinicians are asked to prescribe medicines that they have no experience or knowledge of
- currently there is not a shared care arrangement for the use of Samsca® in the management of SIADH
- it could take several days for a blood result to be reported back to General Practices which would make this difficult for GPs to monitor and respond to sodium changes
- the use described was in a potentially 'brittle'/complex patient group
- the dynamic nature of the condition under consideration, and the need for regular monitoring and dose changes [potentially frequent] based on an individual's sodium levels
- that use was potentially 'long-term' and may involve an 'off-label' dosage regimen, and both scenarios were not considered at the previous meeting
- the Group accepted the difficulties/problems of logistics (prescribing and supply) for people that did not live near to main hospital sites
- the current classification 'recommended for hospital use only' does not prevent supply of medicines by Primary Care, e.g. use of hospital-based prescription (HBP) stationery
- the Group agreed that the Primary Consultant (person that has asked for advice from Endocrinology) is responsible for the care of these complex patients
- if people have frequent admissions, this highlights that they are high risk patients that require regular follow-up

At this time, the Group was not minded to change the classification of Samsca® to allow prescribing in Primary Care. The Group considered that due to the lack of specialist experience in the use of Samsca® and the dynamic nature of the management of patients (regular monitoring and potential for regular change in dose) this is not a simple discharge situation. The Group agreed that the Primary Consultant should take responsibility for the monitoring and prescribing of Samsca® for the patient with complex needs.

The Group unanimously agreed that the classification should remain 'recommended for hospital use only'.

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4. MATTERS ARISING CONTINUED

4.2. SMC 2128 RIVAROXABAN 2.5MG TABLETS

The Group discussed the additional information requested from Medicines Information regarding the trial data for rivaroxaban 2.5mg tablets, when used in combination with acetylsalicylic acid (aspirin) for the prevention of atherothrombotic events in adult patients at high risk of ischaemic events with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD).

Ms Doney confirmed that:
- most Health Boards in Scotland have not included rivaroxaban 2.5mg tablets on their formularies
- Greater Glasgow and Clyde has made it available only for a niche of patients with both CAD **and** PAD
- a request for formulary inclusion has been received and the submission is awaited

Mr Rore discussed his review document and highlighted the main concerns regarding the potential underestimation of bleeding risk.

He confirmed that:
- interpretation of the data is complicated by the fact that there is a trial embedded within the trial [trial of patients also taking a proton pump inhibitor]
- the use of combination rivaroxaban plus aspirin in elderly patients represents a significant bleeding risk
- it was not possible to capture the rate of gastrointestinal bleeds from the data

The Group noted that:
- the addition of rivaroxaban to aspirin increased the incidence of major bleed
- the HAS-BLED Score in these patients [over 65 years and on aspirin] would potentially be high enough to preclude use of rivaroxaban plus aspirin
- rivaroxaban is licensed for this indication so it has proven some benefit and safety
- the combination treatment will be prescribed in Primary Care. How would clinicians continually reassess bleeding risk? Requires individual risk assessments for patients.
- in Cardiology, the greater the level of antiplatelet and anticoagulant treatment the better the patient outcome in term of CAD, but as you increase the agents used to block platelets and coagulation, the greater the harm in terms of risk of bleeding
- gastrointestinal bleeding is life threatening especially in an elderly population
- this would be an example of shared decision making between the patient and clinician, with a full discussion about risks and benefits of treatment
- any bleed, including minor bleed, would involve clinical contact and disruption for patients, e.g. haematuria requiring dip-stick test

The Group highlighted changes required to Mr Rore's paper. When updated the paper will be shared with the requestor.

The Group reiterated its previous concerns that there is a risk of confusion with the licensed doses for the treatment of non-valvular atrial fibrillation, deep vein thrombosis and pulmonary embolism.

Actions:
- Mr Rore will update the paper in line with comments from members, to allow sharing with the requestor — **CR**
- Ms Doney will contact the requestor to highlight the need for clarity about the patient group that is expected to benefit/be treated with rivaroxaban 2.5mg plus aspirin (is it a tightly defined patient cohort where the balance of benefit outweighs the balance of harms – individual clinical assessment) — **FD**
- the requestor will be invited to a meeting to discuss the formulary submission — **FTeam**

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5. FORMULARY GROUP DECISIONS JULY 2019 - PUBLISHED 30/07/2019

5.1. FORMULARY GROUP DECISIONS JULY 2019

Members ratified the decisions of the July 2019 meeting as published.

6. NETFORMULARY/FORMULARY REVIEW

6.2. MELATONIN

The Group noted the availability of newly licensed melatonin products.

The Group noted:
- in NHS Grampian there is a significant spend on melatonin products [circa. £500,000]
- that melatonin is most frequently prescribed for children but there is some use in adults
- Slentyo®:
  - is a prolonged-release melatonin preparation, and is the first product licensed for use in children
  - is indicated for the treatment of insomnia in children and adolescents aged 2-18 years with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient
  - is available as 1mg and 5mg tablets and the cost is significantly higher than the current preferred formulary preparations
- in August the SMC issued provisional advice advising that Slentyo® is not recommended for use in NHS Scotland. The advice is based on a full submission, the submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC. Additionally the company did not present a sufficiently robust clinical and economic analysis.
- another melatonin (immediate-release) product has also been licensed, however it is not licensed for use in children, and is not on the SMC work programme
- that with the availability of additional licensed products the unlicensed melatonin products have been removed from the Scottish Drug Tariff (SDT)
- there are already two melatonin products included on the formulary
- the Director of Pharmacy previously issued a holding statement
- the Medicines and Healthcare products Regulatory Agency (MHRA) does not recommend "off-label" use of products, if a UK licensed product can meet the clinical need, even off-label, it should be used instead of an unlicensed product
- this is the first time we have had a melatonin product licensed for use in children

The Group considered that:
- there is need for robust guidance for prescribing of melatonin, that includes advice regarding maximum dose and starting, stopping, and review criteria
- there is potentially a degree of prescribing creep with prescribing without advice from specialists and used in adults [without complex needs]
- melatonin should not be considered an alternative to short-term prescribing of a benzodiazepine/Z-drug
- the scenario of licensed medicine coming to market but not accepted for use in NHS Scotland is an issue for all Health Boards in NHS Scotland

The Group requested a definitive statement from the Grampian Area Drugs and Therapeutics Committee (GADTC) regarding prescribing of melatonin, noting the not recommended statement from SMC, and potential for increased financial burden with the introduction of the newly licensed melatonin products. **FD/JMcL**

6.3. SBAR – BOWEL CLEANSING PREPARATIONS

The Group discussed the SBAR requesting formulary inclusion of a non-formulary macrogol-based bowel cleansing preparation. The request was to allow audit of practice, and the outcome of the audit would be used to support current practice or a service change.

It was confirmed that:
- the Service would like to evaluate a specific macrogol-based product, Moviprep®
- it is unusual for a medicine to be included on the formulary to allow an audit/evaluation of practice, however it is not unprecedented

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- there is no evidence to support the use of one bowel cleansing preparation over another
- Picolax® and Klean-Prep® are currently included on the formulary, with Picolax® the preferred agent
- Healthcare Improvement Scotland highlight that NHS Grampian is an anomaly in preferring a picosulfate-based product rather than a macrogol-based product for bowel-cleansing
- there is a suggestion that the incomplete bowel clearance rate is higher for Picolax® but evidence for this is lacking, however other Health Boards that have changed product have found it to be a positive change
- the change from Picolax® to a macrogol-based product will increase prescribing costs

The Group noted that:

- the request to use Moviprep® was a service evaluation, where the change in practice that is being evaluated has no specific standard for audit but the completion rate is being used as an outcome
- it is not obvious why Moviprep® has been chosen as the preferred preparation, there is already a macrogol-based preparation on the formulary, Klean-Prep®
- some of the failure rate could be a patient issue not a product issue; patients not taking a product correctly, including incorrect timing of dose
- there may be a slightly reduced risk of hypovolaemia, hyponatraemia with Moviprep®

The Group was not clear how the change in practice would be assessed/audited, however it was reported that for screening colonoscopies, the completion rate is reported nationally.

The Group agreed that the request for a change in product to allow service evaluation was not unreasonable. It noted that there is no significant evidence for the use of one product over another, but that other Boards have had positive results from a change in product. However, it was not clear why Moviprep® was being chosen as the preferred product.

The requestor will be contacted to confirm why Moviprep® is being chosen for evaluation and how the result of evaluation will be reported to the Group. **FTeam**

7. OTHER BUSINESS

7.1. SIGN 158 BRITISH GUIDELINE ON THE MANAGEMENT OF ASTHMA

The Group noted publication of SIGN 158 British guideline on the management of asthma.

7.2. EMA UPDATED RESTRICTIONS FOR FINGOLIMOD PUBLISHED JULY 2019

The Chairman highlighted the publication of European Medicines Agency updated restrictions for fingolimod. The article notes that fingolimod should not be used by women of childbearing age unless they are on appropriate contraception, it should not be used during pregnancy.

7.3. CANNABIS-BASED MEDICINAL PRODUCTS – NICE DRAFT GUIDANCE CONSULTATION

The Chairman highlighted that the NICE draft guidance consultation for Cannabis-based medicinal products is available for comment. The consultation closes 05/09/2019.

8. NEW PRODUCT REQUESTS

8.1. FG1SMC 2138 – LENVATINIB (ADVANCED OR UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC))

There were no declarations of interest recorded in relation to this product.

The Group considered the request for lenvatinib as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy.

The Group noted:

- lenvatinib:
  - is the second multikinase inhibitor licensed for first-line use in this indication. The

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starting dose is based on the patient's weight, 8mg (as two 4mg capsules) once daily for patients with a body weight of <60kg and 12mg (three 4mg capsules) once daily for patients with a body weight of ≥60kg.
  - is an alternative to sorafenib, and the trial showed that lenvatinib was non-inferior to sorafenib [as a first-line option for this indication]
  - is an alternative oral treatment option given once a day compared to sorafenib tablets which are taken twice a day
  - [for this indication] meets SMC end of life and orphan equivalent criteria
- that all secondary efficacy endpoints showed a statistically significant improvement compared with sorafenib; median progression-free survival for lenvatinib was longer than sorafenib [7.3 months (5.6, 7.5) vs 3.6 months (3.6, 3.7): p <0.00001]
- the increase in incidence of hepatocellular carcinoma (HCC)
- that only the 4mg capsules are licensed for hepatocellular carcinoma [lenvatinib is also available as a 10mg capsule strength]
- that dosing is quite unusual in that the starting dose is weight-based but subsequent dose adjustments are only needed to manage toxicities and not for body weight changes during treatment
- the SMC advice takes account of the benefits of a PAS that improves the cost-effectiveness of lenvatinib
- there will be additional costs incurred as patients have the potential to remain on treatment longer than sorafenib

The Group accepted the restricted local need for lenvatinib as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy, as outlined in SMC 2138.

SMC 2138 – Lenvatinib 4mg hard capsules (Lenvima®)▼ is routinely available in line with national guidance (SMC 2138).
Indication under review: as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy.
In a phase III study in patients with unresectable hepatocellular carcinoma who had not received treatment for advanced disease, lenvatinib was non-inferior to another multikinase inhibitor for overall survival.
This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of lenvatinib and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower. It was classified 1b – available for restricted use under specialist supervision and 8b – recommended for hospital use only. Treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. **FTeam**

9. SCOTTISH MEDICINES CONSORTIUM PROVISIONAL ADVICE - ISSUED AUGUST 2019

The Group noted the SMC provisional advice issued August 2019.

If the negative SMC recommendations and non-submission statement are published next month, these medicines will not be included on the formulary for the indications in question. **FTeam**

10. SCOTTISH MEDICINES CONSORTIUM PRESS STATEMENTS - PUBLISHED AUGUST 2019

The Group noted the SMC advice published August 2019.

Following publication of the negative SMC recommendations, for lumacaftor/ivacaftor (Orkambi®)▼ SMC 2182 and tezacaftor/ivacaftor (Symkevi®)▼ SMC 2183, and the non-submission statements, for lenalidomide (Revlimid®)▼ SMC 2217, perampanel (Fycompa®) SMC 2218, pomalidomide (Imnovid®)▼ SMC 2219 and rucaparib (Rubraca®)▼ SMC 2221, these medicines will not be included on the Grampian Joint Formulary for the indications in question.

The following SMC accepted medicines have not been processed within a 60-day timescale:
- SMC 2166 venetoclax (Venclyxto®)▼ (submission expected)
- SMC 2167 tildrakizumab (Ilumetri®)▼ (submission expected)

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- SMC 2169 buprenorphine (Buvidal®) (submission expected)

Local advice for these medicines and indications will be included in the August 2019 decisions as 'Not routinely available as the ADTC is waiting for further advice from local clinical experts'. **FTeam**

FG1SMC 2188 – INOTERSEN (HEREDITARY TRANSTHYRETIN AMYLOIDOSIS (HATTR))

There were no declarations of interest recorded in relation to this product.

At the July meeting, the Group agreed that, due to the change in process of access to ultra-orphan medicines, it is inappropriate to request a formulary submission for highly specialist 'legacy' SMC accepted ultra-orphan medicines, where patient numbers are expected to be exceedingly low, unpredictable or sporadic.

The Group agreed that inotersen is a highly specialist medicine for a very rare condition and that it would be recorded as not routinely available in NHS Grampian, however, if a local need is identified the medicines would be available for use.

SMC 2188 - Inotersen 284mg solution for injection in pre-filled syringe (Tegsedi®) ▼ is not routinely available for use in NHS Grampian.
Indication under review: for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).
In a phase II/III study of adults with hATTR and polyneuropathy, inotersen was associated with significantly less worsening compared with placebo, measured by the change in modified neuropathy impairment score +7 (mNIS+7) and in Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire from baseline to 66 weeks.
This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of inotersen and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.
This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.
Not routinely available in NHS Grampian. **FTeam**

FG1SMC 2172 – PERAMPANEL (REFRACTORY PARTIAL ONSET EPILEPSY)

There were no declarations of interest recorded in relation to this product.

The Group reviewed the abbreviated SMC advice for perampanel (Fycompa®) noting that:
- the oral solution is a new formulation of a formulary medicine
- the indication in SMC 2172 is in line with the current formulary approval for perampanel tablets – for use as a second-line adjunctive treatment in patients with refractory partial onset epilepsy

The Group accepted the restricted local need for perampanel oral suspension, in line with the current formulary acceptance for the oral dosage formulation, without the need for a full submission.

SMC 2172 - Perampanel 0.5mg/mL oral suspension (Fycompa®) is routinely available in line with national guidance (SMC 2172).
Indication under review: for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in adult and adolescent patients from 12 years of age with epilepsy.
Restriction: use as a second-line adjunctive treatment in patients with refractory partial onset epilepsy who are unable to swallow perampanel tablets. Treatment should be initiated only by physicians who have appropriate experience in the treatment of epilepsy. It was classified 1b - available for restricted use under specialist supervision and 8d – treatment may be initiated in the community on the recommendation of a consultant/specialist. **FTeam**

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FG1SMC 1236/17 – EMPAGLIFLOZIN/LINAGLIPTIN (TYPE 2 DIABETES MELLITUS)

There were no declarations of interest recorded in relation to this product.

The Group agreed that Glyxambi® will not be included on the formulary as it is a fixed dose combination product that includes a non-formulary medicine (linagliptin).

SMC 1236/17 - Glyxambi® 10mg/5mg, 25mg/5mg film-coated tablets (empagliflozin/linagliptin) is not routinely available as local clinical experts so not wish to add the medicine to the formulary at this time.
Indication under review: in adults aged 18 years and older with type 2 diabetes mellitus:
- to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Glyxambi® do not provide adequate glycaemic control
- when already being treated with the free combination of empagliflozin and linagliptin
Restriction: restricted to use in line with the previous SMC advice on empagliflozin and linagliptin.
In patients for whom this combination is appropriate, empagliflozin/linagliptin (Glyxambi®) offers a single tablet at a lower cost per dose compared with the individual components.
Not routinely available as local clinical experts so not wish to add the medicine to the formulary at this time. **FTeam**

11. GENERAL INFORMATION FROM SMC AUGUST 2019 - NONE

12. DOCUMENTS FOR INFORMATION

ITEMS 12.1 (MHRA DRUG SAFETY UPDATE JULY 2019)

Ms Davie highlighted the article '*Febuxostat (Adenuric): increased risk of cardiovascular death and all-cause mortality in clinical trial in patients with a history of major cardiovascular disease'*. She confirmed that General Practices in NHS Grampian have patients enrolled in the FAST Study, which is a study that involves the use of febuxostat or allopurinol. However, when the investigators were contacted regarding the new prescribing advice [for febuxostat], it was unclear if patients are being advised of the increased cardiovascular risk now identified with the use of febuxostat.

It was confirmed that:
- the FAST Study [Febuxostat versus Allopurinol Streamlined Trial; an interventional randomised trial] is conducted in General Practices
- at a Practice level, identification of people enrolled in the FAST Study will only be possible if the General Practice has proactively coded patients as being enrolled in the study
- the FAST study investigators are supplying febuxostat or allopurinol to enrolled patients

The Group noted that:
- Healthcare professionals are now advised to avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate
- the inclusion criteria for the FAST study specifically comprises patients with at least one cardiovascular risk factor, including those that have suffered a previous cardiovascular event (myocardial infarction, cerebrovascular accident or transient ischaemic attack)
- if the prescribing advice is not highlighted to patients and actioned appropriately by the trial organisers this puts the caring clinician in a situation where they may be inadvertently going against the best advice for their patients [because the caring clinician is unaware that the patient enrolled in the FAST study is taking febuxostat]

The Chairman asked for confirmation of the organisation(s) that provided ethical approval for the FAST Study. **FTeam**

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	The Chairman will write to the FAST Study organisers regarding the prescribing restrictions for febuxostat that now advise against use in a subgroup of the FAST study patient population, and request clarification of how this is communicated to relevant enrolled patients and General Practices.	JMcL
	The Chairman will discuss this issue with the local Research and Development Director, Professor Maggie Cruickshank, with a view to clarifying how best practice is ensured for studies that are run out of area but involve NHS Grampian General Practices to identify study patients.	JMcL
	Items 12.2 (ADTCC Newsletter July 2019), 12.3 (Medicines Guidelines and Policies Group (MGPG) minute May 2019), 12.4 (Grampian Primary Care Prescribing Group minute March 2019), 12.5 (Antimicrobial Management Team minute November 2018), 12.6 (Antimicrobial Management Team minute May 2019), and 12.7 (MedWatch Newsletter August 2019) were noted.	
13.	**AOCB - NONE**	

DATE OF NEXT MEETING

Tuesday 17 September 2019 starting at 14:30 in the Seminar Room, David Anderson Building.

CHAIRMAN'S SIGNATURE _____ **DATE 17 September 2019**