**Developing a Therapeutic Framework – Report Form**

Name of Student

Defined Area of Practice

1. **Therapeutic use in specified clinical conditions**

This section covers resources that you would use to understand the therapeutics of managing the condition(s) in your clinical area(s). This would be standard textbooks and reviews (ideally evidence based) in more recent educational and peer reviewed journals. In addition this would cover resources such as the BNF, and electronic library of health.

**Section 1a: References relevant to your therapeutic area**

*Include a reference list of articles or books relevant to your therapeutic area. This would include WEB link to on line reviews and articles. You should own copies of these papers/books or have downloaded copies e.g. as PDF*

*(Please extend this list as required for the number of references required)*

Reference 1:

ASHELY C, DUNLEAVY A (eds.), *The Renal Drug Database*. [online] Taylor and Francis Group, Abingdon, Oxford. Available at:

<http://renaldrugdatabase.com/> (accessed 15/01/2016)

What you have learned:

Includes information on dosing in renal impairment of varying degrees and in patients undergoing renal replacement therapies. Provides both Cockroft-Gault and eGFR online calculators and advice on assessment of renal function. Offers key points to consider for interactions and side effects of particular relevance to patients with impaired renal function. The UK Renal Pharmacy Group compiles the information based on SPCs, ongoing systematic review and safety updates and the information provided can differ from the advice given in the licensed product literature. Imatinib, nilotinib and dasatinib included, but not the newer tyrosine kinase inhibitors. Requires subscription with username and password for access.

Reference 2:

<http://www.medscape.com>. Accessed 27th February 2016.

<http://emedicine.medscape.com/article/297664-overview>. Accessed 27th February 2016.

What you have learned:

Medscape –A comprehensive website with access to current clinical information, news and continuing education material for use by healthcare professionals including pharmacists. (Free following registration).

Very useful article giving an overview and links to pages covering background of the definition and origin of the term COPD, pathophysiology and aetiology and treatments although some of the investigations and treatments are from an American angle.

Reference 3:

LYNES, D., 2007. *The management of COPD in primary and secondary care: an introduction.* Keswick: M&K Update.

What you have learned:

Useful comprehensive textbook focused on COPD signs and symptoms, disease process, diagnosis and management. Emphasises the multi-disciplinary approach needed for care of these patients and holistic approach. Last updated 2007 so the pharmacology section may be a little out of date and will need to be used in conjunction with the current NICE guidelines and other up to date evidence.

Reference 4:

Longmore, M. Wilkinson, I. Baldwin, A. Wallin, E. (2014). *Oxford Handbook of Clinical Medicine*. 9th ed. Oxford UK: OUP Oxford. Pages 154-195.

What you have learned:

This is a great book for looking up and interpreting tests. Ranges are given, the purpose of each test given and an explanation of what to look out for (red flags). This is general medicine as opposed to specifically related to respiratory disease; however the respiratory sections are an excellent quick reference without unnecessary repetition. Also, the vast majority of patients (especially COPD/emphysema/bronchiectasis) have several comorbidities and other potential issues – frequently pulmonary. The pages specific to Chest Medicine are 154-195 (Chapter 4).

Reference 5:

HOFFBRAND, A. and MOSS, P. (2016) Chronic Myeloid Leukaemia. In: HOFFBRAND, A. and MOSS, P. *Hoffbrand’s Essential Haematology*. 7th ed. Chichester: Wiley-Blackwell, pp156-164.

What you have learned:

A text book intended for medical undergraduates. Includes an overview of CML covering clinical features and treatment, giving a description of the mechanism of action and side effects of the main medicines used and the definition of response to first line treatment. Also includes an explanation of the laboratory methods used in diagnosis and monitoring, such as karyotyping and FISH analysis.

**Section 1b: Summary of the therapeutic use of drugs**

*Summarise the therapeutic use of the drugs that you will prescribe using the headings below. (Please extend this list to cover all the groups of drugs and drugs in your scope).*

Drug group and individual agents:

Nilotinib

Notes on evidence-based indications:

* Licensed indications in therapeutic area:
* Newly diagnosed Ph+ CML in the chronic phase.
* Chronic phase and accelerated phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
* (Not licensed for blast crisis or other non-CML indications.)

Notes on contraindications and drug/drug and drug/disease interactions:

* No contraindications except hypersensitivity to active substance or excipients, including lactose.
* Caution in patients who have or are at significant risk of developing QT-interval prolongation, e.g. patients with congenital long QT prolongation, patients with uncontrolled or significant cardiac disease, patients taking anti-arrhythmic medication or medicines with known potential to prolong QT, and in presence of hypokalaemia or hypomagnesaemia.
* Patients with risk factors or a history of cardiac disease should be monitored carefully for clinical signs or symptoms of cardiac dysfunction as they are at increased risk of cardiac adverse reactions.
* Caution in patients with history of pancreatitis.
* Not recommended in breast-feeding (low exposure but high risk to baby) Not recommended in conception or pregnancy due to toxicity – there is good evidence that in chronic CML in good response for 2 years nilotinib can be put on hold for the duration of pregnancy. This would require referral to and close monitoring by a consultant haematologist.
* Diabetic control can *worsen* while on nilotinib.
* No dose change required for renal insufficiency.
* Hepatically metabolized therefore use with caution in liver impairment.

Drug group and individual agents:

Inhaled Corticosteroid (ICS) e.g. budesonide, beclometasone, fluticasone, ciclesonide.

Notes on evidence-based indications:

The steroid is the mainstay of asthma treatment (BTS Step 2). A LABA is added if the patient needs Step 3 treatment. LAMAs can also now be used as add-on to ICS+LABA.

Notes on contraindications and drug/drug and drug/disease interactions:

Hypersensitivity reactions; oral thrush; bone density decreased long term, which leads to osteoporosis due to the increased cortisol levels.

Drug group and individual agents:

Imatinib

Notes on evidence-based indications:

* Licensed indications in therapeutic area:
* Newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
* Patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
* (Also licensed for other non-CML indications)

Notes on contraindications and drug/drug and drug/disease interactions:

* No contraindications except hypersensitivity to active substance or excipients.
* Not recommended in breast-feeding (low exposure but high risk to baby).
* Not recommended in conception or pregnancy due to toxicity – there is good evidence that in chronic CML in good response for 2 years imatinib can be put on hold for the duration of pregnancy. This would require referral to and close monitoring by a consultant haematologist.
* Caution for cardiac disease and risk factors for heart failure (increased risk of fluid retention) and hepatic dysfunction (metabolized by the liver - close monitoring of LFTs and FBC required).
* Diabetic control can *improve* while on imatinib.
* No dose change required for renal insufficiency.

1. **Evidence-based Research and Guidelines**

In this section you are building the evidence base behind the medicines you prescribe. Include primary research and systematic reviews such as meta- analysis and Cochrane reviews. Primary research papers should mostly be the most important studies that have provided evidence to inform the guidelines. In table b include the guidelines themselves whether these be national or local, including reference to NICE. Include the WEB links to any on-line material.

**Section 2a: Guidelines**

*Please describe local national and international guidelines that underpin your scope of practice. (Please extend this list as required for the number of references required)*

Reference:

BYRNE JL, HUNTER A, LYTTELTON M (2013) *East Midlands Cancer Network Guidelines for the Investigation and Management of Patients with Chronic Myeloid Leukaemia*. [online] East Midlands Cancer Network. Available at: <http://www.eastmidlandscancernetwork.nhs.uk/Library/EMCNDC000809CMLGuidelinesv3.pdf> (accessed 18/11/2015).

Brief description and what you have learned:

The local Cancer Network (EMCN) guidelines used in my Trust by the local tri-Trust network haematology multidisciplinary team (MDT) to guide treatment decisions. Produced locally through the Haematology Network Site Specific Group (Haem NSSG) consisting of Consultant Haematologists, with input from the multidisciplinary team.

Advocates discussion at Haematology MDT of all newly diagnosed chronic phase CML patients and those requiring change in therapy due to intolerance, failure to respond or progression. Also recommends enrolment of patients on a suitable trial if available locally.

Note that the review date for this document is February 2015 and that it is based on 2009 (not 2013) European LeukemiaNet (ELN) recommendations and on NICE Technology Appraisals available in 2013.

Reference:

<http://www.ers-education.org/guidelines.aspx>. Accessed 20th February 2016.

Brief description and what you have learned:

European Respiratory Society (ERS) website includes European guidance and published research from the European Respiratory Journal. Also provides links to other guidance including NICE guidelines.

**Section 2b: Systematic reviews**

*Please detail below a list the relevant systematic reviews. (Please extend this list as required for the number of references required)*

Reference:

APPLETON, S., JONES, T., POOLE, P., PILOTTO, L., ADAMS, R., LASSERSON TOBY, J., SMITH, B. and MUHAMMED, J., 2006. *Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease.* John Wiley & Sons, Ltd.

Brief description and what you have learned:

This review considered 11 studies (3912 patients, comparing at least 1 month of therapy. Only small benefits of SAMA (ipratropium) over a SABA was seen in terms of lung function, quality of life and reduction in requirement of oral steroids. Combination therapy of SAMA and SABA improved lung function slightly, small reduction in requirement of oral steroid and no effect on quality of life. The authors suggest the advantage of ipratropium compared to a SABA is small so a SABA should be used initially over a SAMA. Again this mete-analysis looked at a range of drugs within the SABA class including nebulised and inhaled so difficult to compare directly all treatments as nebulised doses are much higher than inhale doses. Three of the studies looked at salbutamol and ipratropium. The authors recognise the limitations of the short studies included in the meta-analysis and also the need to compare with LABAs and LAMAs.

**Section 2c: Primary research papers**

*Please describe references for primary research papers. (Please extend this list as required for the number of references required)*

Reference:

Boscia, J. Pudi, K. Zvarich, M. Sanford, L. Siederer, S. Crim, C. (2012). Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clinical Therapeutics*. 34 (8), Pages 1655-1666.

Brief description and what you have learned:

## This trial assessed the once daily dose of fluticasone furoate, the ICS molecule used in the new Relvar Ellipta. This compared outcomes to current treatment i.e. twice daily administration of a combination inhaler containing fluticasone propionate (Seretide) with the outcomes of using once daily administration of the fluticasone furoate molecule (Relvar). The outcomes showed that the once daily dose was non-inferior in terms of therapeutic outcomes. The study suggests that patient adherence/compliance may be improved with once daily versus twice daily dosing. I agree with this aspect for a large number of (but not all) patients. Studies like this allowed for acceptance of the GSK portfolio of Ellipta products. Relvar Ellipta is used in asthma and COPD (lower dose 92/22 only in COPD due to increases in phenomena cases seen with 184/22).

**Section 2d: Summary notes on drugs that you will prescribe**

*Summarise information relating to the drugs that you will prescribe using the headings below. (Please extend this list to cover all the groups of drugs and drugs in your scope).*

Drug group and individual agents:

LABA + LAMA

Notes on evidence-based issues:

LAMA alone is the first element of many COPD pathways, including that in Northern Lincolnshire. However, regions with more advanced/experienced teams are tending towards the use of a LABA+LAMA first line. This is because there are very few side effects associated with the addition of a LABA. Any breathlessness, particularly on awakening, is improved with the addition of a LABA and the devices are the same (very effective DPI and MDI options). The economic impact of adding the LABA is cost neutral. The two active components are always prescribed in a combination device. This is to improve compliance, make technique easier to explain and to keep expenditure well controlled. DPI = dry powder inhaler and MDI = metered dose inhaler i.e. aerosol.

Drug group and individual agents:

PPI (Proton Pump Inhibitor)

Notes on evidence-based issues:

This is used as part of reflux therapy. Reflux is not to be confused with heartburn or indigestion. The correct amount of acid in the correct place is needed. However, due to several factors including diet and physiological changes, respiratory patients experience effects of reflux. PPIs can either be given as a once daily or twice daily dose depending on the severity and timing of symptoms. The aim is the lowest dose at once daily (usually morning) to control the symptoms. Higher doses are usually needed for the first 4-8 weeks of treatment and then further assessment is made.

1. **Adverse Effects, Pharmaceutical Public Health and Pharmacoeconomics**

In this section you will focus on the adverse effects of the prescribed medicines, as the beneficial effects are covered in the evidence-based research guidelines. Consider what the common and rare adverse effects are. Pharmaceutical public health involves gathering the generic ‘public health’ information relevant to your prescribing area. How much is included will depend on your prescribing area, for instance, if you are involved in prescribing in an area that has direct impact on public health, e.g. primary prevention of cardiovascular disease, then that would warrant more information. On the other hand, if you are prescribing very expensive medicines then more on economics might be available.

**Pharmacoeconomics.** This will describe factors such as the cost/benefit, cost/ effectiveness, cost/utility and risk/benefit analysis

**Section 3a: Reference sources**

*Please detail below a reference list of articles or original papers. Where relevant you can include bulletins from health organisations / trusts. (Please extend this list as required for the number of references required).*

Reference:

National Cancer Institute (2010) *Common terminology criteria for adverse events (CTCAE) version 4.0* [online] U.S. Department of Health and Human Sciences. Available at: <http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf> (accessed 13/02/2016)

Brief description and what you have learned:

Defines adverse events in terms of severity and level of intervention required, as well as impact on activities of daily living. Necessary to provide standardisation of description of adverse events when considering safety and tolerability of TKIs.

Reference:

HOFFMAN, V.S. et al (2015) The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European countries. *Leukemia,* 29, pp1336-1343.

Brief description and what you have learned:

This is a non-interventional study taking sample data from the European Registry of CML set up by the European LeukemiaNet.

Median age was 56 years. 55.5% of patients had co-morbidities, mainly cardiovascular (41.9%). The estimated number of new cases of CML per year in Europe is about 6370 (raw incidence 0.99 per 100 000/year) of which 95% were in the chronic phase. The rate of high-risk patients by risk score were 24.7% (Sokal) and 11.8% (EUTOS). The study compared its results to the baseline characteristics of patients in key trials and demonstrated acceptable similarities.

The prevalence of CML is not well known but is estimated to be 10-12 per 100 000

population. This fits with local figures as KGH serves a population of around 300K and has 35 current patients receiving TKIs for CML. The incidence for KGH would be expected to be 3 new patients each year.

Reference:

RODRIGO, G.J., NANNINI, L.J. and RODRÍGUEZ-ROISIN, R., 2008. Safety of long-acting beta-agonists in stable COPD: a systematic review. *Chest,* **133**(5), pp. 1079-1087.

Brief description and what you have learned:

A systematic review already referenced in Section 2. I will specifically describe here the adverse effects described in the paper. The review found that there was no significant difference in respiratory deaths between LABAs and placebo.

**Section 3b: Summary notes on drugs that you will prescribe**

*Summarise information relating to the drugs that you will prescribe. (**Please extend this list to cover all the relevant groups of drugs and drugs in your scope).*

Drug group and individual agents:

SABA

Notes on public health issues and patterns of local use:

SABA (e.g. salbutamol) use is high. This is due to several factors including high pollen rates (rapeseed fields), industrial pollution and large low-lying expanses across the region.

Notes on adverse drug reactions (specify type A or B):

This stimulates the beta adrenoceptors and stimulates sympathomimetic responses. Therefore, side effects can include shaking and nervous feelings, especially if higher doses are used. This is a Type A ADR.

Drug group and individual agents:

Imatinib

Notes on public health issues and patterns of local use:

At KGH 22 out of 35 CML patients are on imatinib (63%). The proportion on imatinib first or second line is not known.

Notes on adverse drug reactions (specify type A or B):

Common side effects:

* Headache
* Nausea – can be reduced by taking with food
* Diarrhoea – can be chronic
* Rash, pruritis – use of moisturisers may help prevention
* Muscle cramps and aches
* Fatigue
* Periorbital oedema
* Peripheral oedema
* Myelosuppression

Imatinib has not been shown to cause significant long-term vascular adverse events and may even have beneficial vascular effects. Imatinib can lower blood glucose, cholesterol and triglycerides.

1. **Clinical Monitoring and Medicines Management**

*Use this section for anything that might be generically termed ‘Patient monitoring’ this would include any reference concerning the clinical monitoring of the patient. Also in this section you can include references to any medicines management issues and in particular adherence.*

**Section 4a: Reference sources**

*Describe below a reference list of articles of original papers or clinical guidelines. (Please extend this list as required for the number of references required)*

Reference:

[www.bloodref.com/myeloid/cml](http://www.bloodref.com/myeloid/cml) (accessed 06/02/2016)

Brief description and what you have learned:

Online risk score calculators for CML to determine prognosis based on pre-treatment investigations. The EUTOS score can be used to predict 18month complete cytogenetic response (CCyR) and 5-year progression-free survival (PFS) rates based on imatinib treatment. The Sokal and Hasford scoring systems were validated for parameters at diagnosis for treatment with busulfan and interferon alfa respectively.

It is important to be aware of these different scoring systems as they do not correlate exactly with each other. Comparing trials looking at the response of patients stratified into a high risk category can be hampered when different risk scores are used.

Reference:

[www.bash.org.uk](http://www.bash.org.uk) Last accessed 21st Dec 2015.

Brief description and what you have learned:

The British Association of the Study of Headache – a resource to help diagnosis headaches, migraines etc. and give the most appropriate treatment options. Some guidelines need slight updates e.g. I disagree with the inclusion of diclofenac and domperidone, but overall they are excellent clear yet in depth guides.

Reference:

<http://real.educationforhealth.org/>. Accessed 20th February 2016.

Brief description and what you have learned:

The Respiratory Education and Learning (REAL) Respiratory Clinic developed by Education for Health and endorsed by the Primary Care Respiratory Society (PCRS). Contains e-learning case studies including diagnosing new patients with COPD and long term management. Case studies reflect UK guidelines. Good to learn about monitoring requirements including spirometry (FEV1 and FEV1/FVC ratio), patient history taking of symptoms and observations from clinical examination and blood results.

Reference:

BRANFORD, S. et al. (2008) Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. *Blood*, 2008, 112 (8), pp3330-3338.

Brief description and what you have learned:

Describes the problem of inter-laboratory variation in molecular analysis and impact on clinical interpretation and comparison of results between clinical trials.

The IRIS trial (see section 2) established the values for molecular response in terms of log reduction in BCR-ABL1 ratio. Other trials have used these milestones but without using the same laboratory there is wide variation (up to 10-fold difference) in the reported values.

The World Health Organisation approved standard international reference materials for quantitation of BCR-ABL translocation by real-time quantitative polymerase chain reaction (Q-PCR) in November 2009 following work by the International BCR-ABL Standardization Group (WHITE, H. et al. (2010) Establishment of the first World Health Organization International Genetic Reference Panel for quantitation of BCR-ABL mRNA. *Blood*, 2010, 116(22), e111-e117).

Reference:

Raghunath, A. Innes, A. Norfolk, L. Hannant, M. Greene, T. Greenstone, M. Morice, A. (2006). Difficulties in the Interpretation of Lung Function Tests in the Diagnosis of Asthma and Chronic Obstructive Pulmonary Disease. Journal of Asthma, Informa Healthcare. 42 (1), Pages 657-660.

Brief description and what you have learned:

This explains the lung function tests that are commonly used and how many conventional tests that only address peak flow and FEV1 etc. may not provide the necessary information to make a complete and informed decision. This paper looks at spirometry and specifically which ratios to use in which patient cohort.

Reference:

Chrystyn, H. Price, D. (2009). What you need to know about inhalers and how to use them. *Prescriber*. 20 (12), Pages 47-52.

Brief description and what you have learned:

A detailed overview of inhaler technique. This helps professionals develop their practical understanding so that they can clearly and logically explain this to patients. Many respiratory professionals, including Henry Chrystyn consider inhaler technique to be the main reason for poor control. From a medicines optimisation perspective, correct technique would mean that ‘step downs’ could happen in asthmatic patients (as per BTS Guidelines), which would not only lead to cost effective prescribing, but also better outcomes for patients in terms of the long-term side effects of prolonged high-dose ICS use.

Reference:

NOENS, L., VAN LIERDE, M., DE BOCK, R. et al (2009) Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*, 113 (22), pp5401-5411.

Brief description and what you have learned:

This was a prospective, observational, non-interventional study which showed that sub-optimal response was correlated to increasing levels of non-adherence to imatinib. One-third of patients were shown to be non-adherent. The authors discuss the factors affecting adherence and advise that non-adherence must be ruled out as a possible cause of lack of optimal response before switching to another TKI.

The study was very small and only carried out over a short (90-day) period, and made heavy use of statistical methods.

**Table 4b: Summary notes on drugs that you will prescribe**

*Summarise information relating to the drugs that you will prescribe. (Please extend this list to cover all the relevant groups of drugs and drugs in your scope).*

Drug group and individual agents:

ICS

Examination skills and professional resources required:

* Spirometry
* Inhaler Technique
* Patient history: exacerbations, SOB, control as defines by BTS. Peak flow is rarely needed except in simple cases as other than seasonal progression or ICS action, this does not give accurate diagnosis (most commonly just improved technique for the peak flow meter).
* Oximeter should also be used, especially in patients showing some level of obstruction (determined from spirometry results). Useful in all patients as the test is quick and simple.

Parameters that need monitoring e.g. plasma levels:

* Patient history is most important, rather than treating numbers. Spirometry can show where problems arise and worsen over time and can also give a good indication or reversibility or any signs or obstructions (which can happen in asthmatics, especially those who are affected into late adulthood).
* For patients on long term ICS, bone density may be monitored (especially in older patients).
* Forced expiratory volume in 1 second – FEV1
* Forced vital capacity – FVC
* Vital capacity – VC
* Ratios of FEV1:FVC and FEV1:VC – depending on condition, age etc.
* All these can be repeated post SABA for reversibility testing.
* Saturated oxygen tests – SATS (94-98% normal range). Less than 92% suggests hypoxemia and requires same day referral and continued monitoring. Less than 88% requires immediate emergency referral and action (e.g. domiciliary oxygen).

**Appendix 1: Useful links**

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| --- | --- |
| <http://www.bmj.com> | British Medical journal |
| <http://www.clinicalevidence.org> | Clinical Evidence – Excellent site from BMJ Journals with useful links to most evidence based sites in the world |
| <http://www.medscape.com> | Medscape –This provides pharmacists and other healthcare professionals access to up to date clinical information, news and continuing education material. (Free following registration). |
| <http://www.sign.ac.uk> | Scottish Intercollegiate Guidelines Network (SIGN) Various clinical guidelines |
| <http://nice.org.uk> | National Institute for Clinical Excellence (NICE) –Technology appraisals and guidance issued for NHS implementation in England and Wales |
| <http://mtrac.co.uk> | Midland Therapeutic Review and Advisory Committee (MTRAC). Reviews of new drugs on the market |
| <http://eguidelines.co.uk> | Guidelines will require you to register to get a user name and password the first time you access these guidelines from the publishers of Medendium, Guidelines and Guidelines in Practice. Organises NHS-commended guidelines by disease area and lists sources |
| [www.medicines.org.uk](http://www.medicines.org.uk) | Electronic Medicines Compendium Allows access to Summaries of Product Characteristics and Patient Information Leaflets of licensed medicines available in the UK |