Evaluation of antiviral prophylaxis of cytomegalovirus in patients receiving liver, kidney or pancreas transplantation

A partial fulfilment of the Norwegian degree

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Abstract

Background – All solid organ transplanted patients are treated with immuno suppression medications to keep the immune system from rejecting the transplanted organ. Unfortunately the suppressed immune system makes the body more exposed for cancer and opportunistic infections. Among the most important viruses that causes one of these opportunistic infections is cytomegalovirus (CMV). A local project showed that not all transplanted patients on CMV prophylaxis get the right dose according to creatinine clearance (CrCl), and that the patients who had not been prescribed the recommended dose according to CrCl had a higher incident of CMV disease than those adjusted as recommended. The Quality improvement team for the transplant unit therefore suggested that a project could further investigate these issues.

Aim and objectives – The aim of this project was to critically review and evaluate the processes in the prescribing and administration of valganciclovir for cytomegalovirus prophylaxis in liver, kidney or pancreas transplantation.

Methods – Semi-structured one-to-one interviews with 2 nurses and 6 prescribers were conducted to establish current practice in prescribing, administration and monitoring of valganciclovir. A review of the local protocols at the transplant unit was conducted. To assess the harm a database analysis on the incident reporting system and a retrospective review of clinical records of 4 patients was undertaken. A questionnaire was developed for staff to self-assess the risk of harm of the whole process of CMV prophylaxis treatment. Pharmaceutical care issues relevant to CMV prophylaxis were recorded prospectively by clinical pharmacists over a two month period.

Results – The semi-structured interviews with prescribers indicated that: 1) Prescribers often fail to recognise that the valganciclovir dose should be adjusted with changing CrCl. 2) That the laboratory test results taken at the clinic do not come back until the evening and are therefore not available at the time of prescribing, 3) There are gaps of knowledge, especially in the junior doctors. Reviews of local protocols suggested a need for update of the protocols and inclusion of detailed dosing guidance. The one incident reported in the database in terms of valganciclovir involved a missed dose. Case note reviews of four patients identified that dose adjustments are appropriate in 2 cases, 1 case was borderline and the other was a complex case but was judged to be appropriate. The questionnaire identified that there was agreement among healthcare professionals that there is a risk of errors that might lead to harm associated with all stages of valganciclovir use. Two clinical pharmacists recommended adjustment of valganciclovir 12 times in 7 patients in a time period of approximately two months.

Conclusion – the outcomes from the interviews and pharmaceutical care issues analysis confirm the previous observation that the dose of valganciclovir is not always adjusted according to CrCl. Recommendations for improvement are to ensure modified guidelines are implemented to ensure all prescribers are aware of need for dose adjustment. Further work can be undertaken to measure the benefit after implement of the recommendations to assess improvement.

Abbreviations

CMV	-	Cytomegalovirus
CrCl	-	Creatinine Clearance
EBV	-	Epstein-Barr virus
eGFR	-	Estimated Glomerular filtration rate
GP	-	General Practitioner
HBV	-	Hepatitis B virus
HCMV	-	Human Cytomegalovirus
KD	-	Katherine Davidson
KP	-	Kinjal Patel
MDR	-	Modification of Diet in Renal Disease
MMF	-	Mycophenolate Mofetil
NHS	-	National Health Service
OPD	-	Out-Patient Department
RIE	-	Royal Infirmary of Edinburgh
SKP	-	Simultaneously Kidney/Pancreas
SOT	-	Solid Organ Transplanted
SPSA	-	Scottish Patient Safety Alliance
SPSP	-	Scottish Patient Safety Programme

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1 Introduction

1.1 Organ Transplantation

Organ transplantation can be lifesaving for many patients with irreversibly damaged organs. Example of organs that can be replaced are kidney, liver and heart.[1]A transplanted organ is often referred to as a graft. UK figures from 2008-9 demonstrated that of 3513 organ recipients, 2552 received an organ from a deceased donor, and 961 from a living donor. Five year kidney graft survival rates are reported as 89 % for transplant from living donors, and 83 % from both deceased heart beating donors (HBD) and deceased non-heart beating donors (NHBD). The patient survival rates following deceased heart beating donor liver transplantation are 90% after one year and 76% after five years. For pancreas the one year graft survival rates are 70%, for simultaneous kidney and pancreas (SPK) transplants the one year rates are 89%. [2]

The Royal Infirmary of Edinburgh (RIE) performs kidney, liver and pancreatic transplantations. According to the annual report for East of Scotland Renal Transplantation Service there were 83 renal transplants with cadaver donor and 26 renal transplants with living donors performed at RIE in 2009-2010.[3] NHS Blood and Transplants (NHSBT) annual statistics showed that 667 liver transplantations with deceased donor were done in the UK in 2008-2009. Five hundred and thirty seven patients got a whole liver transplanted. There were also 27 living liver lobe donor transplants. Nineteen of these transplants were in pediatric patients and 8 in adult patients. NHSBTs statistics also showed that 171 pancreas transplants with a deceased heart beating donor were performed in 2008-2009, but out of these transplantations 131 patients were SPK transplants.[2]

Kidney transplantations are the most frequent type of transplantations performed in the UK.[2] Some of the most common reasons people need kidney transplantation is renal failure due to diabetes and hypertension.[4, 5] Liver transplant is the second most frequently performed.[2] The main reasons for needing a liver transplant are end stage liver disease due to hepatitis C cirrhosis or alcoholic cirrhosis. [6] Pancreas transplantation can be done on people diagnosed with type-1 diabetes, but because the risk with this major surgery and the immunosuppressant drugs can be worse than living with diabetes, pancreas transplantation is therefore not standard treatment. Pancreas transplantation is usually performed in combination with kidney transplantations in patients with severe kidney damage, often caused by diabetes.[7, 8] In both kidney and pancreas transplantation the patient's own organs are not removed from the body. [7, 9]

1.2 Immuno suppression

The immune system protects the body from harm by destroying foreign bodies. Unfortunately, the immune system cannot separate the harmful bodies such as bacteria and viruses from the transplanted organ which is also foreign to the body. To keep the immune system from destroying the organ, transplant patients are prescribed immuno suppression medications[10]. Hence the incidence of graft rejection in transplanted patients has been reduced. Unfortunately, the use of immuno suppressants also comes with serious side effects such as increased risk of infections and cancer. Immuno suppression agents can be divided into various groups depending on their mechanism of action. To increase the immune suppressant effect and reduce the side effects the various groups are usually combined. [10] It is important to not suppress the immune system too much but to maintain a balance. Too much suppression would cause a higher than necessary risk of infections and cancer. When

the body has a suppressed immune system it can be infected with ordinary bacteria, viruses, fungi and some pathogens which do not usually affect people with normal immune systems, these are called "opportunistic infections". Among the most important virus that causes one of these so called opportunistic infections is cytomegalovirus (CMV).[10]

1.3 Cytomegalovirus

Cytomegalovirus (CMV) belongs to the herpes viruses-family. Once a person is infected with CMV, he will always have CMV in his body.[11] Transmission occurs from direct person-to-person contact, via body fluids.[12] The prevalence to CMV is close to 100 percent in developing countries[13], while in the United states between 50 and 80 % of adults will be affected with CMV by the time they reach 40.[14]

Most of the time the virus will be inactive, but it can be reactivated and cause CMV-disease. Reactivation may happen as a result of either a disease like cancer or AIDS, or it can happen due to treatment with immune suppressive drugs or chemotherapy. CMV is for most people harmless, but for immune compromised patients, for example people on immunosuppressant drugs, it can be deadly.[15] The virus can attack different body parts as for example oesophagus, stomach, intestine, lungs or eyes. Symptoms that may appear in patients with CMV disease can be fever, night sweats, weakness, sore throat, fatigue, and swollen glands. [16]

An organ transplantation with a CMV-positive donor can cause a CMV-negative recipient to develop CMV disease, and a reactivation in a those recipients who already are CMV-positive. Despite the risk in transplanting a CMV-positive organ, this is not contraindicated and is adopted in practice due to a high prevalence of CMV in the population and shortage of

organs. Recent studies also show that implementation of effective antiviral prophylaxis treatment can give a successful outcome. [17, 18]

1.4 CMV prophylaxis and treatment

1.4.1 Choice of prophylaxis agent

Ganciclovir and valganciclovir, a prodrug for ganciclovir, remain the most used treatment options for prevention and treatment of CMV disease, even though they are expensive and toxic. Aciclovir and its prodrug valaciclovir are both used less frequently for CMV prophylaxis in solid organ transplant (SOT) patients. Some studies show little or no benefit from prophylaxis with aciclovir in renal transplant patients. This means it may be used in recipients with low risk CMV profile. It is not effective in liver patients.[19] Foscarnet and cidofovir are used for treatment of active CMV disease if the patient does not respond to ganciclovir treatment, but are less used alternatives because of renal toxicity.[20] They are not recommended for treatment of CMV infections other than retinitis in AIDS patients.[21, 22]

Studies comparing efficacy and safety of valganciclovir against oral ganciclovir of CMV prophylaxis show that valganciclovir has no superior efficacy only that it causes more neutropenia compared to other agents.[23, 24]

A randomised, prospective, double-blind, double-dummy study compared the efficacy and safety of valganciclovir with oral ganciclovir as CMV prophylaxis in 364 SOT patients where the recipients were CMV- negative and the donors CMV-positive. Two hundred and thirty nine patients was randomised to the valganciclovir group and 125 patients randomised to the ganciclovir group. End-points analyzed included were if the patients developed CMV disease, acute rejection and safety of valganciclovir. The endpoints were checked after 6 and 12 months. CMV disease developed in 12.1% of valganciclovir patients and in 15.2% of

ganciclovir patients by 6 months. By 12 months, the incidences were 17.2% in valganciclovir patients and 18.4% in ganciclovir patients. Acute allograft rejection was lower with valganciclovir. After 6 months 29.7 % of the valganciclovir group had experienced acute graft rejection, compared to the ganciclovir group with 36 %. After 12 months the difference between the two groups had decreased. For valganciclovir the percent was 32.6 and for ganciclovir 35.6%. The safety profile was similar for both drugs except from the incident of neutropenia which was higher in valganciclovir patients (8.2 %) than in ganciclovir patients (3.2 %). The researcher conclusion was that "valganciclovir was as clinically effective as oral ganciclovir with a comparable safety profile"[23]

A meta-analysis of CMV prophylaxis in solid organ transplanted (SOT) patients compared valganciclovir with other agents, mainly ganciclovir. The background for this study was that the writers suspected that valganciclovir was not more efficient or safer than the other treatment alternatives, despite it being most the commonly used and the most expensive. The results from this analysis did not find that valganciclovir was more efficient than the other treatment therapies, but it did find that the risk for neutropenia and CMV late-onset disease was higher with valganciclovir.

The research group behind the study suggest several reason for valganciclovir popularity: "The reasons for this popularity are multifactorial, including the convenience of once daily dosing, limitations on the production of oral ganciclovir, and influential marketing strategies by the manufacturer."[24]

Table 1 CMV prophylaxis and treatment options in SOT patients[19]

Drug	Prophylaxis	Treatment
Ganciclovir (IV)	✓	✓
Valganciclovir (oral)	✓	✓
Aciclovir	✓	
Valaciclovir	✓	
Cidofovir		✓
Foscarnet		✓

1.4.2 Treatment duration

An international, randomized, prospective, double-blinded study was conducted to compare prophylaxis treatment with valganciclovir for 200 days with treatment for 100 days in CMV negative patients who had received a CMV positive graft. Two years after they had been transplanted, CMV had occurred in 21.3% of the group that was treated for 200 days, while among the patients treated for 100 days 38.7% developed CMV disease. One hundred percent of the patients treated for 200 days survived compared to 97 % in the other group. The rates of graft loss and acute rejection rates were comparable in both groups. The 200-day group had acute rejection in 11.6% of the patients vs. 17.2% for the 100 days group. The graft loss rates were 1.9% for the 200 days group and 4.3% in the 100-days group. The research group concluded that "Extending valganciclovir prophylaxis from 100 to 200 days is associated with a sustained reduction in CMV disease up to 2 years post transplant." [25] Six months prophylaxis with valganciclovir together with a one-time determination of viremia have shown to be cost effective compared to three months prophylaxis. [26]

No other agents for CMV prophylaxis is specifically licensed for treatment for 200 days, but the SPC to valaciclovir states that the treatment may need to be extended beyond 3 months and the costs were therefore compared to the costs of valganciclovir 200 days. The expenses were lower for the valaciclovir treatment. [27]

1.4.3 Complications with present treatment option.

As mentioned earlier CMV is an important problem in SOT patients. The increased accessibility of antiviral therapies has reduced the development of CMV disease, but it has also caused other problems such as ganciclovir resistance, late-onset CMV disease, and insecurity about most favourable treatment duration of CMV prophylaxis and treatment. [28]

A study conducted on SOT recipients and the emergence of ganciclovir-resistance CMV disease showed that 2.1 % of the SOT recipients in the study developed ganciclovir-resistant cytomegalovirus disease. Five out of 67 (7%) CMV-negative recipients who received a CMV-positive organ developed a CMV disease with resistance against ganciclovir. None of the 173 CMV-positive recipients developed ganciclovir-resistant CMV disease.[29]

A study was conducted in 2001 regarding prevalence on late onset CMV disease. The study showed that most of the CMV disease episodes happened between 3 and 6 months post transplantation. The study included 37 liver and kidney transplanted patients. The recipients were CMV-negative with CMV-positive donors and they were treated prophylactically with oral ganciclovir 100 days after transplantation. The probabilities of acquiring CMV disease were 0% at 3 months, 23.7% at 6 months and 27% at 12 months.[30]

There is general agreement that prevention is the best treatment option against CMV in solid-organ transplants recipients, but all the antiviral treatment options are more or less toxic. A

solution may be development of a vaccine.[28] Several CMV vaccines are in various stages of development, but none are currently available.[31]

1.4.4 Valganciclovir

Valganciclovir is absorbed from the gastrointestinal tract and quickly metabolised to ganciclovir. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine. Ganciclovir is phosphorylated to ganciclovir triphosphate and inhibits viral DNA synthesis by competing with deoxyguanosine triphosphate. Ganciclovir triphosphate is incorporated into viral DNA, Viral DNA elongation is terminated and replication of herpes viruses is inhibited. [32, 33] Viruses sensitive for this drug include Human Cytomegalovirus (HCMV), Epstein-Barr virus (EBV), hepatitis B virus (HBV) and several of the herpes viruses. For patients who have received a solid organ transplant, the recommended dose is according to the SPC 900 mg once a day, starting within 10 days of transplantation and the treatment should last until 100 days post-transplantation and 200 days in kidney-transplantation. Most of the drug is eliminated through renal excretion and the elimination is an important factor for interactions with other drugs [32] Ciclosporin and tacrolimus, which are used as immuno suppressant agents in transplanted patients, can impair kidney function[34, 35] and therefore placing patients at risk of toxicity from renal excreted medicines. Mycophenolate mofetil (MMF) competes with ganciclovir for tubular secretion and may increase concentrations of both substances.[36] Both of these types of interactions can lead to excessive exposure of ganciclovir and may be associated with serious adverse reactions. Severe leucopoenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been associated with use of valganciclovir. Therefore, patients with renal impairment must have the dose adjusted according to renal function estimated by measurement of creatinine

clearance.[32] To decrease risk of toxicity regular haematological monitoring should also be undertaken to minimise risk of harm. CrCl can be calculated by the Cockcroft-Gault equation:

Equation 1: Cockcroft-Gault Equation[37]

$$CrCl(^{ml}/_{min}) = \frac{(140 - \text{age[years]}) \times \text{Bodyweight(kg)} \times 1{,}04(\text{female}) \text{or } 1{,}23\ (\text{male})}{\text{Serum Creatininee}(\mu\text{mol/L})}$$

Table 2 shows how the doses should be adjusted according to the calculated CrCl.

Table 2: Dosage adjustments according to creatinine clearance in renal impaired patients.[32, 38]

CrCl (ml/min)	Valganciclovir dose for prophylaxis against CMV disease
≥ 60	900 mg (2 tablets) once daily
40 – 59	450 mg (1 tablet) once daily
25 – 39	450 mg (1 tablet) every 2 days
10 – 24	450 mg (1 tablet) twice a week
< 10	100 mg three times a week after dialysis (liquid solution)

Special precautions should be taken when handling this medicine. If tablets are crushed or broken they should be thrown away in special waste. Staff should not come in direct contact with the broken tablets because the tablets are considered possibly carcinogenic and

teratogenic. If direct contact should occur the person should wash thoroughly with soap and water.[32]

1.5 Guidelines

All guidelines are designed to minimise the potential for harm, but there is concern that in practice such guidelines are not closely followed. Reviews of methods for changing healthcare behaviours, indicates that mailing guidelines to targeted healthcare professionals and publishing them does not lead to changes in staff behaviour. Less passive methods of dissemination are necessary. It requires time, passion and resources to manage to disseminate and implement clinical guidelines. [39]

If guidelines are not used, there is potential for harm especially when high risk medicines are used. This project will attempt to identify where practice can be improved to minimise harm to transplant patients receiving antiviral prophylaxis for CMV.

The transplant unit at RIE has its own protocol in both liver and renal transplantation

1.6 Scottish Patient Safety Alliance – Scottish Patient Safety Programme

The topic for this project was chosen after discussion with the quality improvement team (QIT) at the transplant ward at RIE. The QIT is part of the clinical governance infra-structure which is in place to facilitate delivery of an organisational quality improvement programme. It integrates with the Scottish Patient Safety Programme (SPSP), which is a national programme developed to improve safety of hospital care in the National Health Service (NHS) in Scotland.[40] Compared to international standards, NHS Scotland provides overall good safety to patients, however, as for any organization, there are still errors happening

which can be avoided. To help address this the Scottish Patient Safety Alliance (SPSA) was established. This organisation co-ordinates the Scottish Patient Safety Programme.[41] A comparable safety programme was initiated in 3000 hospitals in the U.S and this has saved approximately 122,000 lives.[42] Research shows that ten percent of patients admitted to Scottish NHS- hospitals experience adverse events , and 50% of these events are most likely avoidable.[41] One of the tools the SPSP uses to improve the safety is the Model for Improvement.[43] the model has two parts, first it has three questions you should consider:

- What are you trying to accomplish?
- How will you know your change is an improvement?
- What changes can you make that will result in improvement?

The second part is the Plan-Do-Study-Act cycle which is used to test if you have accomplished improvement. First you plan it, then you do it, then you observe the results and at last you act on what you have learned.[43, 44]

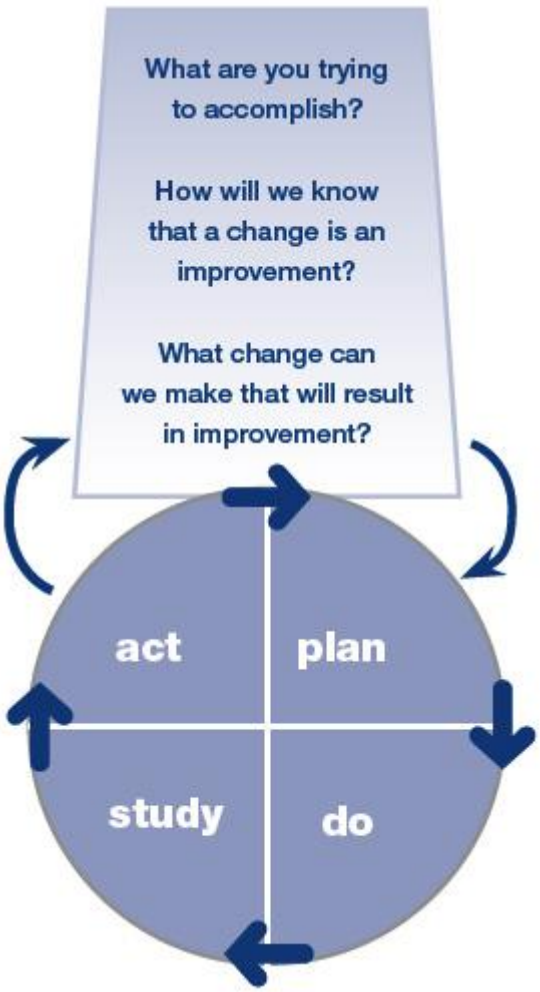

Figure 1 Model for improvement.[43]

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use defines adverse event as: "Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment." [45] Under the term adverse event belongs the term adverse drug event, which the institute of medicine defined as "an injury resulting from medical intervention related to a drug."[46] This can easily be confused with adverse drug reaction, which has the well-accepted definition "A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological

function."[45] To avoid adverse drug events which actually cause harm, medication errors are defined as "Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer" also need to be eliminated.[47] Medication errors are the most common type of medical error happening in facilities. [48] Reducing medication errors will therefore be important to improve patient safety, and to this project.

To eliminate medication errors you first have to identify when during the process incidents happens. The NHS uses an incident reporting system called Datix®. This system helps to map steps where things can go wrong. When reporting an adverse event in Datix® the incident has to be described, the reasons that this incident happened have to be investigated, and what action is taken in this particular case and what action is taken in general to prevent this from happening again need to be documented. Each incident requires information such as lessons learned from the incident, the drug, the severity of the adverse event, where it happened, the reporter and the category of event. Each speciality has a quality improvement team (QIT) which looks at Datix® and initiates measures to prevent adverse events.

A retrospective study was recently conducted in the Netherlands to examine how many of adverse events found in patients' record are reported in the hospital reporting systems. A database from a record review study was used; this included 14 hospitals and 5375 patients. In the records for these patients this research group identified 498 adverse events; only 18 of these events were also found in one or more of the reporting systems they searched through. This show that most healthcare workers unfortunately will not report adverse events into the incident reporting systems .[49] A survey conducted on staff at a nursing home shows that

important barriers for them to report errors are: fear of being blamed, time consuming, lack of recognition that a medication error has occurred and fear of disciplinary action.[50] The NHS needs to encourage reporting and establish several methods for identifying quality improvement opportunities. A study called the CHUMS study - Care Homes Use of Medicines Study financed by the Department of Health in England investigated the prevalence type and underlying cause of errors in care homes. The results from this study showed that there were errors done throughout the whole process. The likelihood that there will be an error when prescribing something is 8.3%, for monitoring the percent is 14.7 %, 9.8 % for dispensing and 8.4 % for administration. In this study prescribing and monitoring errors were picked up by clinical medication review by the pharmacist. Dispensing errors were picked up by visual checking the medicines and administration errors were picked up by observation of drug rounds.[51] In the transplant unit the clinical pharmacist and the pharmacy technicians carry out medication reviews on the patients admitted to the hospital (in-patients) and may pick up prescribing errors. Prescribing errors can also be picked up by other healthcare professionals. Dispensing errors may be picked up by the pharmacist or the pharmacist technician when they do a medication review for patients in the hospital and see review patients own drugs, or by the nurses during administration. There are no checkpoints (points in the process where errors can be detected before causing potential harm to patients) for either administration or monitoring of treatment after the patient is discharged. Some administration errors can be picked up by retrospective review of medicine charts, but not all errors can be detected that way. Errors may be picked up at the next clinic visit.

Clinical pharmacy plays an important role in safe and effective use of medications.[52-55] This was demonstrated in a single-blind, standard care–controlled study which investigated the impact of having a pharmacist present at ward rounds. The results showed that

preventable adverse drug events were reduced by 78 percent.[52] Another study done in an emergency department compared a group of patients where the pharmacist checked the medication orders with a group of patient with no pharmacist. The results was that the rate of errors was 16.09 per 100 medication orders for the control group compared with 5.38 per 100 orders for the intervention group.[53] Also, a systematic review of thirty-six studies was done to evaluate the role of the clinical pharmacist and outcomes on in-patient adults. The review concluded that the addition of clinical pharmacist resulted in improved care and outcomes.[54] A randomized trial was conducted to determine if a pharmacist intervention would improve adherence in heart failure patients. These interventions included providing of verbal instructions and written materials to the patient about their medications. The conclusion of the study was that the interventions could improve adherence, but that the interventions probably had to be done constant to benefit.[55]

Anecdotally it is recognized that pharmacists do not formally document all interventions they make.

The Royal Pharmaceutical Society has made a set of guidelines for recording interventions. They have listed four main reasons for a pharmacist to record interventions they make:

- To ensure and improve patient care.
- To provide evidence that the pharmacists contribution is of value.
- To have a record available for examination on where decisions could be challenged
- And to monitor incidents or near misses in prescribing, dispensing or administration of medicines as part of an organisation's clinical governance framework.[56]

1.7 Why is it important to reduce medication errors?

In addition to the obvious reasons in reducing harm and saving lives, elimination of medication errors can save the NHS a lot of money. The National Patient Safety Agency (NPSA) believes that more than £750 million is used each year in England on preventable harm from medicines [57] A study was conducted on adverse drug events in older patients in ambulatory settings. The study investigated incidence and preventability of adverse drug events. The study showed that most adverse events happened in the steps of prescribing (58.4%) and monitoring (60.8%), and they concluded that "Prevention strategies should target the prescribing and monitoring stages of pharmaceutical care", which is the main focus steps in this project. Among the errors occurring in the prescribing stage were wrong therapeutic choice, wrong dose and not enough education about the medication to the patient. In the monitoring step example of errors found were failure to act on clinical findings or laboratory results and inadequate monitoring.[58]

High risk medicines associated with medication errors have been the focus of many SPSP initiatives such as anticoagulants and insulin.[59] There are many other groups of medicines with potential for optimisation of prescribing to avoid medication errors and harm. Within the transplant unit one of these groups is CMV prophylaxis given to patients who have received an organ transplant. In immune compromised patients it is essential that CMV infection is prevented without toxic effects from the drugs.

An important reason that the QIT suggested the evaluation of the processes of use of valganciclovir as prophylaxis in transplant patients was a local student project done on CMV. The project included 257 patients transplanted from Jan 2006 to May 2009 followed up at 4 different hospitals (The Royal Infirmary of Edinburgh, the Aberdeen Royal Infirmary, Raigmore Hospital in Inverness and Ninewells Hospital in Dundee). One part of this project

investigated if the prescribing of valganciclovir was correct according to CrCl (calculated by the Cockcroft-Gault equation) and how incorrect prescribing affected the incidence of CMV disease. Ninety eight of the 257 (38%) patients in the study used valganciclovir and were included in this part of the study. Seventy nine of them were kidney transplanted patients and 19 of them were simultaneously kidney and pancreas transplanted patients. At discharge, 46 (58%) of the kidney patients received the correct dose according to their CrCl and 33 (42%) of the kidney patients were prescribed incorrect dose according to CrCl. Of the patients who received an incorrect dose 12 (36%) of them developed CMV disease, while only 5 (11%) of those who received the correct dose according to CrCl developed CMV disease. Three months after transplantation 8 out of the 33 (24%) patients who received incorrect doses at discharge still had not had their dose corrected. Two of these developed CMV disease. This study suggested that adjusting the Valganciclovir dose according to CrCl is not always done correctly and this increases the incident of CMV disease.[60]

This project aims to evaluate the processes for prescribing, administrating and monitoring of Valganciclovir in patients who have received liver, kidney or pancreas transplantation with the intention of making recommendations to improve the use of this agent with the intention of improving patient safety.

2 Aims and objectives

2.1 Aim

Critically review and evaluate the processes in the prescribing and administration of valganciclovir for cytomegalovirus prophylaxis in liver, kidney or pancreas transplantation.

2.2 Objectives

1. Define the processes for prescribing, administering and monitoring of valganciclovir use for CMV prophylaxis.
2. Characterise the procedures available to support decisions in the use of valganciclovir.
3. Characterise the harm assessment based on data from audit
4. Investigate problems in the prescribing, administering and monitoring of valganciclovir by interviews with clinical staff.
5. Characterise pharmaceutical care issues from prospective audit of pharmacists' contributions.
6. Critically evaluate opportunities for quality improvement by presentation of findings to an expert group.

2.3 Subjects and settings

2.3.1 Study design

The project comprises semi-structured one-to-one interviews with prescribing staff and nurses, database analysis of reporting system Datix®, retrospective review of pharmaceutical interventions, self administered questionnaire for various healthcare professionals and a review of clinical records.

2.3.2 Subjects and settings

The transplant ward at the Royal Infirmary of Edinburgh has beds for 16 patients, additionally there are 5 beds in the High Dependency Unit (117). There is one team for kidney transplantation, and one for liver. The kidney- team also covers pancreas transplantations. The teams consist of a junior grade doctor, medical registrar, surgical registrar, consultant physician and consultant surgeon. The teams rotate regularly. Prescribers were categorised into junior grade doctors, middle grade doctors and senior grade doctors. The senior grade doctors consist of consultants, the middle grade doctors are registrars, and junior grade doctors are any doctor with less experience than a registrar.

Once discharged patients are followed up in the out-patient clinic and can be seen by clinic nurses, a senior or middle grade doctor and a transplant-coordinator. The clinic runs several times a week for both liver- and kidney-transplanted patients. The frequency of appointments for each patient varies depending on the clinical picture and time since the transplantation.

The project was undertaken in parallel with another student project which investigated prescribing and monitoring the use of immune suppression drugs. The project team consist of the investigator Sara Ann Dyrhaug, investigator for the parallel project Kinjal Patel, clinical supervisors Katherine Davidson and Scott Garden, and academic supervisor Moira Kinnear.

2.3.3 Inclusion criteria

Convenience sampling was chosen to select staff for invitation to participate in interviews. The senior doctors recruited were those the clinical supervisor thought were most likely to agree to participate. The other prescribers and nurses were recruited according to their availability.

Convenience sampling was also used for case note review. Clinic visits by the investigator were fixed and therefore reviews were of patients attending the clinic on these fixed days. Patients who fitted the following inclusion criteria were included:

- Liver transplanted patients: CMV-negative recipient who received an organ from a CMV-positive donor or a re-transplanted patient.

  Kidney/SKP transplanted patients: All transplant recipients except cases where both the recipient and the donor were CMV-negative.

- Valganciclovir indicated for CMV prophylaxis.

- Database recorded incidents reported were analysed for the calendar year 2010. The self-assessment questionnaire was distributed to a convenience sample of staff.

2.3.4 Ethics approval

Approval to conduct the study was sought from the multidisciplinary transplant team and senior Pharmacy managers through submission to both the Pharmacy and Transplant Quality Improvement teams. Confirmation that the project does not require research ethics approval was confirmed from the scientific officer of the South-East Scotland Research Ethics Committee. (Appendix 1)

3 Methods

3.1 Establish current practice in the use of valganciclovir

Mapping the actual process for prescribing, administrating and monitoring the prophylaxis treatment with valganciclovir was done by conducting interviews with nurses and prescribing staff at the transplant ward at RIE. Prescribing staff with different grades of experience in both renal and liver were included. The investigator held a short power-point presentation to make the prescribers at the transplant ward aware of the project. The clinical pharmacist reserved a slot for the presentation in a regular meeting the prescribers attended. Staff participants were recruited by the clinical pharmacists at the liver transplant unit. E-mails were sent out to 5 of the healthcare professionals following verbal agreement, to arrange time and place for the interview for mapping the process and an interview for the student project running simultaneously. The chosen staff had verbally agreed to participate prior to the e-mail was followed up. The interview questions together with the protocol for the project were attached in the e-mail. One of the emailed prescribers did not answer nor participate in the interviews. Time and place for two of the prescribers was arranged through the clinical pharmacists for the renal transplant unit. One of the healthcare professionals who received an email was a charge nurse who arranged for two nurses to participate in the interview, one junior and one senior nurse. The interviews were conducted in quiet places around the ward or in the staff offices. Seven of the eight interviews were scheduled in one week, and one or two interviews were done daily. The last interview was agreed orally between the clinical pharmacist for the liver unit and the person being interviewed. Present at the interviews was the investigator, fellow investigator KP and the person being interviewed. KP had her own interview which was conducted before this interview. The interviews were tape recorded, and

the tapes were transcribed verbatim. A sample of 10 % of the transcript was checked by KP, before the tapes were destroyed to maintain anonymity in accordance with data protection act.

1The questions for the interviews were prepared in advance. There was one set of questions for nurses on administration, and one set of questions about prescribing and monitoring for prescribing staff. (Appendix 3)

3.2 Valganciclovir prophylaxis guidelines

Pharmacy and medical staff confirmed that the guidelines used on the transplant unit at RIE were their own protocols. Both the liver transplant unit and the renal transplant unit have their own protocol.

The renal unit guidelines were found by searching on their homepage (www.edren.org) with the search term "CMV". The protocols for the liver transplant unit were obtained from clinical supervisor KD.

3.3 Characterise the harm assessment based on data from audit

3.3.1 Reported adverse drug events

An e-mail was sent to the quality assurance pharmacist to agree on how to obtain medication incident reports recorded on the database for the transplant unit for the time period of 2010. The investigator received a printed copy. The reports were carefully studied, mainly seeking for reports associated with valganciclovir. The investigator also looked for general errors that could possibly affect this treatment. This could for example be missed doses or administration of wrong drug.

3.3.2 Clinical data from out-patient clinics

The investigator together with a clinical pharmacist visited the out-patient clinic three different days to collect data. Two of those days renal/pancreas transplanted patient visited the clinic and the third day liver transplanted patients had appointments. A list of patients with appointments that day was collected from the clinic desk each of the three days. Patient information such as weight, sex and time since transplantation together with given doses of valganciclovir and communication with GP was collected from their files in the clinic. Date of birth and initials was also collected to allow data be retrieved from a data programme that had laboratory values. The patient's initials and date of birth were removed before investigator left the hospital that day. The patient's creatinine levels and frequency of laboratory monitoring was found through a clinical information computer system. The creatinine clearance was calculated using the Cockcroft-Gault equation, and the appropriate dose recorded. If the appropriate dose did not match the given prescribed, the clinical pharmacist assessed the patients' clinical picture for reasons to justify the dose prescribed. All the data was filled out in a form made in advance. (appendix 6)

3.4 Clinical staff opinions of where there is risk in the process

A questionnaire for staff opinion on risk was developed and reviewed by the project team (Appendix 2). The questionnaire was handed to doctors and nurses at the same time as the interview for mapping the process. The questionnaires were also handed out to two clinical pharmacists at the ward, and one of the clinical pharmacists also handed it out to a transplant coordinator. The questionnaire had listed the whole processes of prescribing, administrating and monitoring in steps. At each step the staff could choose between four categories that they thought described the risk best:

- I think there is a risk of errors that will always lead to harm
- I think there is a risk of errors that might lead to harm in some cases
- I think there is a risk of errors that will never lead to harm
- I think there is no risk of errors (with or without harm as consequence)

There was also a column were they could write in comments. The information given with the questionnaire was that this was to get the staff to assess the risk of harm in each step of the process.

3.5 Pharmaceutical Care Issues

A checklist for the pharmacist to fill out when they made interventions regarding patients on valganciclovir was developed (Appendix 3). Main care issue for the checklist was appropriate dose adjustment of valganciclovir. Two clinical pharmacists at the transplant ward filled out this checklist from the 14th of February until the 11th of April whenever they made interventions relevant for the checklist. There is one clinical pharmacist for the liver transplant unit, and one for the renal transplant unit.

3.6 Opportunities for Quality Improvement

With lack of time being an important issue, the project team decided that the project findings and opportunities for quality improvement were going to be discussed at a meeting with only the project team. /

4 Results

4.1 Current practice in the use of valganciclovir

The interviews with staff helped the investigator map the processes of prescribing, monitoring and administration.

4.1.1 The process of prescribing

The patient criteria for prophylaxis treatment are for liver transplanted patients either that the recipient is CMV-negative and receive a CMV-positive organ, or that a patient is re-transplanted. For kidney/pancreas transplant patients the criteria are that either the recipient is CMV-positive before the transplantation or the donor is CMV-positive. In other words, the only ones that do not match the criteria and are not routinely put on valganciclovir prophylaxis are cases where both the donor and the recipient are CMV-negative. All the prescribing staff agreed on these criteria.

The renal prescribers all agreed that the treatment should be initiated right after the transplantation. Among the liver transplant prescribers there was some uncertainty and disagreement. One of the senior doctors said that it should be written up on one of the two first days, but that it didn't have to be started immediately after transplantation. A possible reason for the prophylaxis treatment to not be initiated immediately after is because the patient might be in intensive care. Another senior said it should be initiated at day seven, and the junior did not know and guessed the day after.

For kidney transplanted patients the treatment duration is 180/200 days. For liver transplanted patients the duration is 90/100 days. Most of the prescribers agreed on the duration, except the two junior doctors who did not know. One of them guessed lifelong treatment.

All prescribers except the renal junior agreed that they decide the dose according to creatinine clearance, which all agreed is calculated by the Cockcroft-Gault equation. The renal junior said he/she used estimated glomerular filtration rate (eGFR) for deciding the dose. Although almost all of them know that the dose should be based on Cockcroft-Gault several of them admitted they do not calculate the dose themselves, but depend on the pharmacist to do it for them.

None of the doctors considered any other factors than the kidney function when deciding the initiating dose. The senior renal doctor could share that none of their transplanted patients had normal kidney function so the doses for all their patients is based only on Cockcroft-Gault CrCl at initiating the treatment.

Only the middle grade doctor had actually used the oral solution, all the others said they used tablets; the senior doctors added that they were aware that there is a oral solution available for patients with difficulties in swallowing or for patients with renal function less than 10 ml/min.

4.1.2 The process of monitoring

For monitoring the therapy several laboratory tests are taken when the patient is visiting the clinic. The patient can have a CMV-PCR (numbers of copies of CMV per millilitre blood) done, but they are not routinely done on patients on CMV prophylaxis unless they have symptoms. One of the senior doctors said he/she would check CMV-PCR after stopping prophylaxis for the two next visits, because that is often when they see CMV-disease develop. They also tend to do CMV testing in patients who are not on prophylaxis who have an unknown illness or unexplained changes in their liver function tests. Another important test is creatinine value so that the CrCl can be calculated. Full blood count and other monitoring of liver function are checked routinely post transplant anyway.

All the prescribing staff agreed that frequency of the laboratory tests monitoring varies with individual patients. The patients are not brought back for CMV monitoring alone, but it depends on their clinical picture. There was some uncertainty among the interviewees about if frequency should be changed after dose alteration among one junior and one senior doctor. Another senior doctor explained that when adjusting doses there are two possible situations for the patients. One of the situations is that the patient who has had renal dysfunction which has improved and the dose has been increased. The patient has become better and the periods between monitoring tend to be extended. The other possible situation is those who have progressed renal dysfunction who will be coming back more frequently as their kidneys appear to get worse. The frequency of monitoring will go up, but that is because of the complete clinical picture and not for valganciclovir monitoring alone.

The senior doctors adjust the dose after CrCl based on the Cockcroft-Gault, although two out of three do not calculate it themselves. Some prescribers mentioned that they have big posters in the OPD (Out-patient department). The poster is made by the company Roche which manufactures valganciclovir. The middle grade doctor uses edren.org and the junior doctors adjust the dose using different types of literature. One of them uses their local protocol. The senior doctors were asked if they would change the dose according to blood tests at one occasion, or if they would wait to see if there is a trend. One prescriber answered that he/she personally thinks one should wait and see if there is a trend. The second one answered that he/she tends to adjust the dose after the level that they are at, but added that you would usually have seen a trend before the patient reached another dose level. The third senior prescriber said that it depends. In some occasions the doctor sees a patient who is right on the edge of moving into the next group and the patient will not come back for the next couple of weeks. It is easier for the patient to get it sorted out then and there. The laboratory results are

taken right before the doctor's appointment at the clinic and will not come back before that evening, so sometimes the prescriber predict that the CrCl will push the patient into the next dose level and changes the dose. Then at evening, when the results come back, the doctor will phone the patient and tell him/her to stick to the dose he/she was on, if the creatinine clearance was not as predicted.

All the doctors said that they communicate with GPs, but that they do not expect them to participate in the monitoring. The patients visit the clinic so often that getting the GPs to do additionally tests would only complicate things. One consultant said that they may ask patients to attend their practise to have full blood count and renal function checked, but the hospital get the results and make the decisions. So the GPs are involved as far as participating with taking blood tests, but they don't expect the GPs to make important decisions regarding valganciclovir or other transplant medications. This communication is documented in letters.

4.1.3 Prescribing and monitoring

One senior doctor said they use the unit protocol which is reviewed every year. Another senior doctor said they use the guidelines from The British Transplant Society. The third senior prescriber said they used guidelines based on Cockcroft-Gault. The middle grade doctor answered that he/she uses www.edren.org. The renal junior said he/she does what the pharmacist tells him/her what to do most of the time, and the liver junior did not know.

The middle grade doctor said he/she follow the guidelines accurately, while the senior doctor said that they are guidelines not rules and that he/she deviates, and the reason for that was past experience.

The prescribers were asked what they do and how they would document it if they discovered a prescribing-error or instances where the treatment is not optimised. One of the senior

doctors only answered on how he/she would document it which was only in written letters. All the other doctors answered that they would correct the error. One senior doctor said he/she would document it in letters. And that they would not discuss it at a m&m-meeting (morbidity and mortality meeting). Another senior prescriber used adjusting the valganciclovir dose as an example. The doctor does not think of it as a prescribing error if someone has failed to recognise the improving function and make a change. The doctor would not record that sort of incident on the database, because the prescriber thought the database would just get overloaded with those kind of reports, because there are too many examples of that. The middle grade doctor would document accurately what had happened, and what he/she is going to do about it. He/She would also communicate either verbally or in writing depending on the urgency on the situation with the relevant people involved. The aim would be to correct it for that patient and minimizing the likelihood of a similar error happening to other patients. One junior doctor said he/she would write in the notes what had happened and if there was any harm to the patient he/she would tell the patient at the same time, so he/she was informed that there has been an error. Also he/she would make sure that all the doctors looking after the patient knew and the consultant was aware. The other junior prescriber said he/she suppose he/she should fill out an incident report about it, because there had been an error. He/She said you should let the senior doctors know, and also the nurse because he/she thought they had their own incident reports to fill out.

4.1.4 The process of administrating

Both of the nurses stated that the doctors are very good at letting the nurses know about new prescriptions, and they estimated that 99 percent of the time they remember to tell them if there is a new drug prescribed for a patient. Ordering for ward stock from pharmacy happens routinely twice a week by trained nurses. This is documented on the pharmacy sheet where

the orders are written. The ordering for individual patients is done by trained nurses or a pharmacist.

On a question on how the drug rounds happens the senior nurse answers that they now use the POD-system (patient's own drugs) where the patient has their medication locked in a bedside locker. He/She said they had an old system were they had a big drug trolley (that contained stock drugs) that made people aware that the nurses are on drug rounds so they would not be disturbed. The nurse is less excited about the new system where he/she can use 90 minutes on six patients compared to the old system were it took her/him one hour to give drugs to the whole ward. The new administration system has come with a few risks, especially since people may not realise that the nurses is on drug rounds. Both of the nurses were positive to the new implementation of tabard that says:"Do not disturb, Nurse on drug round".

The nurses were asked if they are aware of the precautions required for handling valganciclovir. The senior nurse did not, but the junior nurse was aware that gloves should be used when handling this medicine and that you should not come into contact with it, and the gloves have to be put in a special bin after they are used because of its toxicity. He/She says that both the nurses and the pharmacists give this information to the patients.

If there is an administration error both nurses agree that the doctors will have to be notified. The senior nurse says that in 9 out of 10 times this will be discussed with the patient, and that it has to be documented. The junior nurse stated that an incident report has to be filled out on the computer, where it gets sent to people who deal with it.

4.2 Guidelines

The renal/pancreas team at the Royal Infirmary follows their own protocol for CMV prophylaxis treatment. The guidelines are found on their homepage www.edren.org, and the homepage states it was last reviewed December 2009. The patient criteria for CMV prophylaxis are that all patients except CMV-negative recipient with a CMV-negative donor should be treated. The drug of choice is valganciclovir. The treatment is to be initiated within 10 days of transplantation, and continues until 180 days post-transplantation. The dose is adjusted according to creatinine clearance (calculated with Cockcroft-Gault equation) which is a measure for kidney function. This is shown in table 3:

Table 3: Dose adjusted after creatinine clearance in guidelines [61]

CrCl (ml/min)	Valganciclovir dose for prophylaxis against CMV disease
≥ 60	900 mg (2 tablets) once daily
40 – 59	450 mg (1 tablet) once daily
25 – 39	450 mg (1 tablet) every 2 days
10 – 24	450 mg (1 tablet) twice a week
< 10	100mg three times weekly after dialysis (liquid formulation)

Valganciclovir is available in tablets (450 mg) and as an oral solution. The tablets should be administrated with food, and not crushed.

The guidelines also state that full blood count and liver function tests must be monitored daily. A common reason for discontinuing the treatment before the 180 days is over is

leucopenia, which can occur due to treatment with valganciclovir. Post transplant patients are not routinely tested for CMV, but in cases of any illness where CMV is suspected, tests should be run. The handbook suggest CMV PCR, and mentions also that respiratory or other samples can be sent to virology [61]

When searching for CMV within edren.org, one of the search results found was the immuno suppression handbook with a paragraph on CMV prophylaxis. One of the things mentioned was that valganciclovir dosing was according to eGFR. [62]

The liver transplant unit at RIE has their own protocol they follow which are reviewed yearly. The protocol says that high risk recipients with normal kidney function will receive valganciclovir 900 mg daily starting at day 7 after transplantation and continuing until 3 months after transplantation. The dose needs to be adjusted in renal impaired patients. High risk recipients are defined as either CMV-negative recipients who receive a CMV-positive graft or re-transplants.[37]

4.3 Harm assessment based on real data

4.3.1 Collecting data from incident reporting system

In 2010 the transplant ward at RIE had 34 incidents reported in Datix®. Of these reports only one has specified that it concerned Valganciclovir, but 4 of the reports about drug errors had not mentioned which drug the incident concerned. The one report on Valganciclovir was about a missed dose and the seriousness graded as low. This was discovered by medical staff and the patient. The dose was missed due to staff attending a cardiac arrest on another patient. Pharmacist and senior staff were informed.

Three of the four reports which had not mentioned which drug the incidents concerned were in the category of drug not signed for at administration.

Out of the 34 reports, 13 of them concerned missed doses and 5 of them not signing for administration of drugs. It appears in the reports that it can be difficult to choose how to categorise these two because they do not know if the dose is not given or if it is just not signed for. There were also a couple of reports where medication not given yet were already signed for.

21 reports on administration errors, 4 reports on prescribing errors, 4 report on other, 3 on medicine, 1 report on information and 1 not categorized.

4.3.2 Look at real data from a snapshot in the clinic

On the first day of renal clinic 2 out of 12 patients with appointments fitted the inclusion criteria (see 2.3.3). On the second day 1 out of 11 fitted the criteria, and for day 3 only 1 out of 17 were included. The communication with GP for patient 1 was exceptional and the clinical files were updated with the letter sent to GP only 4 days earlier. The clinical files for the rest of the patients contained many letters to the GP and the clinical pharmacist considered the communication with the GP good. The results from the out-patient clinic is summarised in table 4.

Table 4: Real data from a snapshot at the clinic

	CrCl (ml/min)	Calculated dose	Given dose	Time of transplantation	Frequency of lab tests	Justification for not giving calculated dose
Patient 1	55,4	450 mg daily	450 mg every other day	jun.08	Monthly	This patient have been diagnosed with CMV viremia, and cannot be treated after protocol, clinical pharmacist assessed the dose as appropriate
Patient 2	58,7	450 mg daily	450 mg daily	mar.11	2-3 times a week	---
Patient 3	59,4	450 mg daily	900 mg daily	feb.11	Weekly	The previously CrCl was 61.8, and has barely crossed the border between 450 and 900 mg daily
Patient 4	43	450 mg daily	450 mg daily	feb.11	Weekly	---

4.4 Harm assessment from staffs opinion

Table 5 summarizes the opinions of the participating staff on the risk of harm through the whole treatment process for SOT patient.

Table 5: Staffs opinion on risk of harm

	I think there is a risk of errors that will always lead to harm	I think there is a risk of errors that might lead to harm in some cases	I think there is a risk of errors that will never lead to harm	I think there is no risk of errors (with or without harm as consequence)	Comments
Deciding if Valganciclovir should be prescribed	1(nurse)	10			
Deciding when to start treatment	1(nurse)	9	1 (pharmacist)		
Deciding dose for patients with normal kidney function		9		1(transplant-coordinator)	1= Not applicable
Deciding dose for renally impaired patients	2(two junior doctors)	9			
Calculating Creatinine clearance	2(junior doctor and nurse)	9			1= Cockcroft-Gault depends on ideal body weight
Choosing correct drug formulation	1(nurse)	8	2 (pharmacist, senior doctor)		
Deciding treatment duration	1(nurse)	9	1 (pharmacist, senior doctor)		
Administering right drug	1(nurse)	10			
Administering at right time		10	1 (senior doctor)		
Adjusting dose after measurement of Creatinine clearance	1(nurse)	10			
Collaborate with GPs on treatment and monitoring		10		1 (senior doctor)	

4.5 Pharmacist Checklist

The pharmacist on the liver transplant unit made 2 interventions regarding the CMV treatment. One of the interventions made was advising to decrease a dose. The other intervention was about initiating valganciclovir prophylaxis. A patient who himself was CMV-negative, received a graft from a CMV positive patient had not been prescribed CMV prophylaxis 9 days after the transplantation. The clinical pharmacist for the kidney transplant team made 13 interventions on 8 different patients regarding the CMV treatment. One patient had valganciclovir written up in their chart, although both he himself and his organ donor were CMV negative. The pharmacist noted this the first day after transplantation. The pharmacist advised to increase the dose 11 times on 6 different patients, and reduce the dose one time on one patient.

4.6 Presenting findings

The results from the project were discussed at a project team meeting and the team agreed that the main finding was that adjusting doses according to CrCl seems to be a problem and action should be taken to propose how to improve this practice.

5 Discussion

5.1 Current practice in the use of valganciclovir

As it emerged in the interviews, not all nurses are aware of the precautions for handling valganciclovir. This drug is as mentioned in the introduction (see 1.4.4) considered potentially carcinogenic and teratogenic, and staff should avoid direct contact with broken or crushed tablets. The lack of knowledge this nurse had about handling medication might not have led to harm, but it is definitely a risk for the nurse. However, with only two nurses included in the project, it cannot be concluded if this is a general problem at the ward.

It also emerged that there are some gaps of knowledge regarding CMV prophylaxis treatment, especially among the junior doctors. The knowledge about this treatment could be improved if either a pharmacist or a senior prescriber routinely held lectures regarding this subject mainly for junior doctors and nurses.

The prescribers do not seem to separate between renal prophylaxis treatment for 200 days and 180 days, or liver prophylaxis 100 days and 90 days. The guidelines say 90 days for liver and 180 days for renal. This was discussed between the investigator and the clinical pharmacist, the clinical pharmacist stated that in practice the treatment is not stopped after exactly 90 or 180 days. Literature is done on all of the above mentioned timeframes (90, 100, 180 and 200 days).[25, 26]

Although not initially thought of when developing the questions, the investigator considered it important to know whether the prescribing doctor waited for a trend before adjusting the doses. Therefore this question was added after the interviews with one junior and one middle grade doctor. The other junior answered that he/she was not in the clinic, so he/she was not

asked this question. It could have been of further interest to have asked the junior/middle grade doctors if they had been taught anything about this from the seniors or if they had opinions on how this should ideally be handled.

The senior prescribers seemed to agree that a trend should be seen before adjusting the dose. One consultant said he/she tends to adjust the dose after the level they were at, but that they usually have seen a trend before the patient reach a new dose level. Although this consultant expressed him/her self a little different than the others, the investigator interprets his/her answers as he/she agree with the other consultants.

One consultant said that he/she initially predicted the dose and adjust the dose after that, then later he/she change it according to the patients actually CrCl when the laboratory tests come back, and then phone the patient to let change the dose back if he/she had predicted the dose wrong earlier. That might be a good way of doing it. Another possibility is that the patient can have his blood tests taken to the GP a few days before their appointment at the clinic. However this arrangement will most likely will not be relevant for patients seen on a weekly basis or more frequently. As the local project showed the titration of dose for this drug is a problem, so measures to improve this treatment better need to be initiated. One idea is that a prompt could be included in the out-patient proforma document as a reminder in case the patient is seen by different prescribers each clinic appointment.

An important weakness for this method is the selection of interviewees. The senior doctors chosen were those the pharmacist thought it was most likely to agree to participate. The staff considered likely to participate were staff considered positive towards the project and might therefore had opinions on the project matter that they would like to get across. The opinions might have been different with other prescribers. On the other hand were the prescribers who

wanted to participate were very honest, this might not have been the case if prescribers with a negative attitude towards the project had been interviewed. They might not have given as honest answers.

5.2 Guidelines

Although the project has a small sample size, the interviews indicate that the renal junior and middle grade prescribers use their protocol and the clinical pharmacist relatively frequently. This became apparent as it was their answers to several of the questions. That implies that it is crucial that the protocols are accurate, easy to understand and leave little room for interpretation. In one part of the renal unit handbook for immuno suppression it is stated that valganciclovir should be adjusted according to eGFR. That might be the reason that the renal junior doctor answered this on how to adjusts valganciclovir dosage. At RIE eGFR is calculated by the modification of diet in renal disease (MDRD) equation. A retrospective, cohort-controlled study compared the use of MDRD versus Cockcroft-Gault equation for renal dosing adjustments in patient with chronic kidney disease. It emerged that there was a significant variability between using MDRD and Cockcroft-Gault.[63] Using eGFR value may not always lead to harm, but it can be a risk. The renal immuno suppression protocol should therefore be reviewed.

The protocol for the liver unit is quite straightforward and easy to understand. The protocol states that the valganciclovir dose should be adjusted according to kidney function. It does however not say how to adjust it or what kidney function test it is dependent on. This might be self explanatory for most prescribers, and they might say they know where to find it if they do not have it in their head. For junior prescribers who perhaps use the protocol more often, it might have been good to have included both the equation and a table with recommended

doses under CMV prophylaxis in the protocol. A concern was that the liver junior doctor answered that he/she did not know what protocol to use. It was not clear if the doctor just could not remember what guidelines to use at the moment, or if he/she was not aware of the local protocols. It is crucial that the staff is aware of the guidelines, and one way to accomplish this could be to make them available online.

The renal protocol is quite easy to understand and contains a lot of useful information. Unlike the liver protocol, they have included a table over recommended doses depending on CrCl. It does not state that CrCl should be calculated by Cockcroft-Gault, but this was something all the prescribers knew in the interviews, which indicate that this is well known among doctors. Four out of six prescribers said they get the pharmacist to calculate the dose for them, or answered that they do what the pharmacist tells them to when adjusting the dose. One doctor used the edren.org calculator. One thing that would be interesting to find out is why only one out of six prescribers calculate the CrCl themselves? The investigator suspects it might be difficult to find the Cockcroft-Gault equation from a reliable source, as he/she could not find the equation in the protocol for the renal unit, under CMV prophylaxis in the liver unit protocol, or in the SPC[32]

The kidney unit protocol does include the table with dose recommendations according to CrCl, but a more detailed protocol for both renal and liver might have improved the CMV prophylaxis treatment.

The renal protocol also states that full blood count and liver function tests must be monitored daily, this seems impractical for out-patients and the investigators suspects that this information is incorrect. Through the interviews it emerged that the patients do not visit the clinic more often than twice a week. The information might be intended for in-patients or

patients receiving treatment of CMV infection, but that should have been specified. Following this study it is suggested that the renal protocol be reviewed.

5.3 Harm assessment based on real data

5.3.1 Collecting data from incident reporting system

Datix® is very subjective. In the report of missing a valganciclovir dose the incident was graded as low, another incident with missing a dose of another drug was graded as medium. If these reports are done to prevent a similar episode from happening again, then the error of the incident should be graded on the seriousness of the error and be the same grade, and not based on the possible outcome.

If the incident is graded on the patient's possible outcomes then the whole clinical picture for the patient should be explained in detail. This leads on to another limitation, the incident reports varied a lot in length of description and amount of details included. Some reports were one sentence, while others were considerable longer. This may be a result of lack of training (capability) or perhaps lack of time (capacity). It is important that the staff are properly trained in how to report incidents and aware of the importance of prioritising this activity. It has to be clear to the health care professions when they should fill out an incident report, what and how to fill it in, and how to grade the seriousness of the incidents.

As it emerged in the results, most of the reported incidents concerned drug administration. It is therefore important to come up with initiatives to prevent administration errors. The nurses interviewed in mapping the process could also support these findings, and expressed their concern with the constant interruption of nurses on drug rounds.

This might indicate that only administration errors are occurring, however this is not very likely. We may therefore assume that the nurses are better at reporting incidents. The reasons that other health care professions is not reporting might be lack of time, fear of being blamed and personal opinion that it is a waste of time.

One interesting finding was that the Datix® reports do not include any reports on up titration of valganciclovir as the renal function increases. One of the senior doctor said there are so many examples of prescribers failing to recognize that the dose should be increased that Datix® would be full of these kinds of reports. Also the pharmacist interventions where 11 of 15 interventions made were up titration suggest that this is a problem. Reason to why they are not reported may be as the senior prescriber does not regard this as a prescribing error. Another possibility might be that they just do not report incidents in Datix®. If the incident reports were used by practitioners themselves as a learning tool and were seen to be useful, perhaps they would be used more often.

5.3.2 Look at real data from a snapshot in the clinic

This method was meant to actually prove if there are problems regarding adjusting valganciclovir dose according to creatinine clearance, but the sample size of patients meeting the criteria and being checked became much smaller than anticipated. By only looking at four patients it is impossible to conclude with anything, but after visiting the clinic three times time did not allow to collect more data in this project.

A future project could be to investigate this with a larger sample size. A strength with this method was that the investigator had a clinical senior pharmacist to help assess each case. Some patients had complications and could not be treated using the standard protocol.

Unlike prescribing and monitoring this treatment for in-patients have different kinds of staff as a checkpoint, monitoring the therapy for out-patients have no checkpoint. Maybe it could have been possible for the pharmacist to check medications in out-patients, especially patient on valganciclovir.

5.4 Harm assessment from staffs opinion

What the results of this questionnaire do tell, is that most staff thinks there is a risk of harm in all the steps in the process. Although most staff have answered that they think there is a risk of harm in some cases, in most of the steps, it is interesting that juniors and nurses are the only ones who have graded something as "**I think there is a risk of errors that will always lead to harm"** and only consultants, coordinators and pharmacist has graded things as **"I think there is a risk of errors that will never lead to harm"** and **"I think there is no risk of errors (with or without harm as consequence)".**

The questionnaire might have been interpreted in different ways. The staff might have thought the questionnaire meant that they should assess the risk of an error to actually reach the patient without anyone picking it up. Or they might have though the questionnaire meant that they should assess the risk of their error leading to harm if it affected the patient.

The outcome might have been better with an interview, the original idea was to ask the staff open questions and let them talk about where they think the risk lay, but time did not allow for this to be done. Conducting interviews are time consuming and instead of having two different interviews in this project, it was decided to use a questionnaire to assess the risk. The questionnaire was developed so that staff had to assess the risk of the whole process, also steps they do not take part in themselves, to see if they had opinions about other health care

professionals work. The plan was that the comment column would be what gave most information from the questionnaire. The investigator thought the staff would state why they checked off as they did, but only two comments were added in one questionnaire out of the 11 that were filled out. The column should not have been called “comments”, but something to get the staff to explain why they crossed off as they did. Another alternative was that the investigator could have given more information about the questionnaire before handing it out. It should have emerged that the aim of this questionnaire was to find out in which steps staff think there is a risk of harm, and why.

5.5 Pharmacist Checklist

The pharmacist interventions indicate that adjusting the doses according to changing CrCl is a problem. This does not necessarily lead to harm for the patient. These interventions are done frequently by the pharmacist and they are in a way a checkpoint to ensure safe medicine use for in-patients. Maybe it could be an idea to use the pharmacist as a checkpoint for out-patients as well.

A weakness about this method was that the checklist could have been better. It should have included the categories: not prescribed when should have been, and prescribed when should not have been. Also the checklist had space for all the needed information to calculate the creatinine clearance, but not the actually given dose. So if the investigator wants to have the information available, all the information should be collected.

Strengths for this method are that the checklist was short and user friendly, which increases the chance of it actually being used. One of the clinical pharmacist who used it was included in the development of the checklist. Only two clinical pharmacists have been used to record

interventions which increases the chance of it being accurately filled out, compared to if many people would have filled it out.

To check if the implementing suggestions have an effect, the Plan-Do-Study-Act cycle could be used. Using this cycle, this project would be the planning, implementing the improvement suggestions would be doing. The study step could be to see if the number of interventions would decrease if the pharmacists recorded interventions for a new period of two months. Another measure of improvement could be to conduct new interviews with junior doctors to see if the knowledge has increased.

6 Conclusions

The aim of this thesis was to evaluate the processes of prescribing, administrating and monitoring the prophylaxis treatment with valganciclovir, and one of the objectives/methods was to make suggestions for improvement.

Several opportunities for improvement emerged through this study. The local protocols are one of them where information should be reviewed to provide accurate detail. Previous work showed that the valganciclovir dose is not always adjusted to CrCl, and that this seems to increase the incidence of CMV disease. The pharmacist interventions and the interviews with prescribers in this project support these findings. It also emerged that there were gaps of knowledge regarding this treatment, especially in junior doctors, and that almost none of the prescribers calculate the appropriate dose themselves.

7 References

1. *World Health Organization, Department of Essential Health Technologies - Transplantation [www.who.int]*. [cited 2011 05.04]; Available from: http://www.who.int/transplantation/organ/en/.
2. *National health service, Blood and Transplant - Transplant acticity in the UK [www.organdonation.nhs.uk]*. [cited 2011 07.03]; Available from: http://www.organdonation.nhs.uk/ukt/statistics/transplant_activity_report/archive_activity_reports/pdf/ukt/transplant_activity_uk_2008-2009.pdf
3. *Renal Unit at the Royal Infirmary of Edinburgh, Scotland - East of Scotland Renal Transplantation Service Annual Report [www.edren.org]*. 2010 [cited 2011 08.04]; Available from: http://www.edren.org/media/download_gallery/TPannreptApr09_Mar10.pdf
4. *National Kidney and urologic disease information clearinghouse- High Blood Pressure and Kidney Disease*. [cited 2011 03.04]; Available from: http://kidney.niddk.nih.gov/kudiseases/pubs/highblood/#how.
5. *National Kidney and urologic disease information clearinghouse - Kidney Disease of Diabetes*. [cited 2011 03.04]; Available from: http://kidney.niddk.nih.gov/kudiseases/pubs/kdd/.
6. *University of Maryland, Medical centre [www.umm.edu] - Reason for liver transplant* 10.09.2008 [cited 2011 05.04]; Available from: http://www.umm.edu/transplant/living_liver_decision.htm.
7. *MedlinePlus - Pancreas transplant*. 05.12.2009 [cited 2011 23.03]; Available from: http://www.nlm.nih.gov/medlineplus/ency/article/003007.htm.
8. *Mayoclinic [www.MayoClinic.com] - Pancreas Transplantation*. 22.09.2009 [cited 2011 22.03]; Available from: http://www.mayoclinic.com/health/pancreas-transplant/MY00762/METHOD=print.
9. *MedlinePlus - Kidney transplantation*. 22.06.2009 [cited 2011 23.03]; Available from: http://www.nlm.nih.gov/medlineplus/ency/article/003005.htm.
10. John, A. *British Transplant Society [www.bts.org.uk] - Immunosuppression* [cited 2011 23.03]; Available from: http://www.bts.org.uk/transplantation/immunosuppression/.
11. *Centers for disease control and prevention [www.cdc.gov] - Cytomegalovirus(CMV) and Congenital CMV infection*. 06.12.2010 [cited 2011 03.04]; Available from: http://www.cdc.gov/cmv/overview.html.
12. *Centers for disease control and prevention [www.cdc.gov] - CDC Home Cytomegalovirus (CMV) and Congenital CMV Infection - Transmission*. 28.07.2010 [cited 2011 09.05]; Available from: http://www.cdc.gov/cmv/transmission.html.
13. Krech, U. and J. Tobin, *A collaborative study of cytomegalovirus antibodies in mothers and young children in 19 countries.* Bull World Health Organ, 1981. **59**(4): p. 605-10.
14. *National Institute of Neurological Disorders and Stroke [www.ninds.nih.gov] - Neurological Consequences of Cytomegalovirus Infection Information Page*. 12.02.2007 [cited 2011 05.04]; Available from: http://www.ninds.nih.gov/disorders/cytomegalic/cytomegalic.htm.
15. *Centers for Disease Control and Prevention weak immunesystem [www.cdc.gov], Cytomegalovirus (CMV) and Congenital CMV Infection - People with Weakened Immune Systems*. 28.06.2010 [cited 2011 04.04]; Available from: http://www.cdc.gov/cmv/risk/weak-immune.html.
16. *MedlinePlus, CMV - immunocompromised host*. 12.01.2009 [cited 2011 08.04]; Available from: http://www.nlm.nih.gov/medlineplus/ency/article/000663.htm.
17. Ginns., L.C., A.B. Cosimi., and P.J. Morris., *Transplantation*. 1999. p. 942.

18. Johnson, R.J., M.R. Clatworthy, R. Birch, A. Hammad, and J.A. Bradley, *CMV mismatch does not affect patient and graft survival in UK renal transplant recipients.* Transplantation, 2009. **88**(1): p. 77-82.
19. *British Transplant Society [www.bts.org.uk] - British Transplantation Society Guidelines for the Prevention and Management of CMV Disease after Solid Organ Transplantation - Third Edition* 2011 [cited 2011 27.04]; Available from: http://www.bts.org.uk/transplantation/standards-and-guidelines/?locale=en.
20. Eid, A.J. and R.R. Razonable, *New developments in the management of cytomegalovirus infection after solid organ transplantation.* Drugs, 2010. **70**(8): p. 965-81.
21. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Foscavir*. 28.09.2010 [cited 2011 05.03]; Available from: http://www.medicines.org.uk/EMC/medicine/174/SPC/Foscavir/.
22. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Vistide*. 07.04.2011 [cited 2011 08.04.2011]; Available from: http://www.medicines.org.uk/EMC/medicine/1585/SPC/Vistide/.
23. Paya., C., A. Humar., E. Dominguez., K. Washburn., E. Blumberg., B. Alexander., et al., *Efficacy and Safety of Valganciclovir vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in Solid Organ Transplant Recipients.* American Journal of Transplantation, 2004. **4**(4): p. 611-620.
24. Kalil, A.C., A.G. Freifeld, E.R. Lyden, and J.A. Stoner (2009) *Valganciclovir for Cytomegalovirus Prevention in Solid Organ Transplant Patients: An Evidence-Based Reassessment of Safety and Efficacy*. **4**.
25. Humar, A., A.P. Limaye, E.A. Blumberg, I.A. Hauser, F. Vincenti, A.G. Jardine, et al., *Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study.* Transplantation, 2010. **90**(12): p. 1427-31.
26. Luan, F.L., L.J. Stuckey, J.M. Park, D. Kaul, D. Cibrik, and A. Ojo, *Six-month prophylaxis is cost effective in transplant patients at high risk for cytomegalovirus infection.* J Am Soc Nephrol, 2009. **20**(11): p. 2449-58.
27. *Scottish medicine [scottishmedicines.org.uk] - Valganciclovir*. Available from: http://www.scottishmedicines.org.uk/files/advice/valganciclovir_Valcyte_FINAL_DECEMBER_2010.doc_for_website.pdf.
28. Torres-Madriz, G. and H.W. Boucher, *Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients.* Clin Infect Dis, 2008. **47**(5): p. 702-11.
29. Limaye, A.P., L. Corey, D.M. Koelle, C.L. Davis, and M. Boeckh, *Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants.* Lancet, 2000. **356**(9230): p. 645-9.
30. Razonable, R.R., A. Rivero, A. Rodriguez, J. Wilson, J. Daniels, G. Jenkins, et al., *Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir.* J Infect Dis, 2001. **184**(11): p. 1461-4.
31. Kotton, C.N., D. Kumar, A.M. Caliendo, A. Asberg, S. Chou, D.R. Snydman, et al., *International consensus guidelines on the management of cytomegalovirus in solid organ transplantation.* Transplantation, 2010. **89**(7): p. 779-95.
32. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Valcyte*. 18.06.2010 [cited 2011 05.03]; Available from: http://www.medicines.org.uk/EMC/medicine/9315/SPC/Valcyte+450mg+film-coated+tablets/

33. Buck, M.L. *Ganciclovir and Valganciclovir Use in Children*. 2009 [cited 2011 08.04]; Available from: http://www.medscape.com/viewarticle/712277_2.
34. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Neoral*. 04.02.2011 [cited 2011 08.04]; Available from: http://www.medicines.org.uk/EMC/medicine/1307/SPC/Neoral+Soft+Gelatin+Capsules%2c+Neoral+Oral+Solution/.
35. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Prograf*. 05.08.2010 [cited 2011 08.04]; Available from: http://www.medicines.org.uk/EMC/medicine/11102/SPC/Prograf+0.5mg%2c+1mg%2c+5mg+Hard+Capsules/.
36. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Cellcept*. 27.10.2009 [cited 2011 08.04]; Available from: http://www.medicines.org.uk/EMC/medicine/1679/SPC/Cellcept+250mg+Capsules/.
37. *Scottish Liver Transplant Unit, Royal infirmay - Protocol for in-patient management following liver transplantation.*
38. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Valcyte powder for oral solution*. [cited 2011 10.05]; Available from: http://www.medicines.org.uk/EMC/medicine/21603/SPC/Valcyte+Powder+for+Oral+Solution/.
39. Feder, G., M. Eccles, R. Grol, C. Griffiths, and J. Grimshaw, *Clinical guidelines: using clinical guidelines.* BMJ, 1999. **318**(7185): p. 728-30.
40. *The Scottish Patient Safety Alliance [http://www.patientsafetyalliance.scot.nhs.uk] - The Scottish Patient Safety Programme*. [cited 2011 08.04]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/programme.
41. *Scottish Patient Safety Alliance [www.patientsafetyalliance.scot.nhs.uk] - About the alliance*. [cited 2011 08.04]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/about-the-alliance.
42. *The Scottish Patient Safety Alliance [http://www.patientsafetyalliance.scot.nhs.uk/] - About the Scottish Patient Safety Programme*. [cited 2011 08.04]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/programme/about.
43. *The Scottish Patient Safety Alliance [http://www.patientsafetyalliance.scot.nhs.uk] - Using the model for improvement*. [cited 2011 15.05.2011]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/docs/homepage/data/pages/patientsafetytools/usingmodel.html.
44. *Institute for healthcare improvement [www.ihi.org] - How to improve*. [cited 2011 15.05]; Available from: http://www.ihi.org/IHI/Topics/Improvement/ImprovementMethods/HowToImprove/.
45. *European Medicine Agency - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.* **2011**.
46. Bates, D.W., D.J. Cullen, N. Laird, L.A. Petersen, S.D. Small, D. Servi, et al., *Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group.* JAMA, 1995. **274**(1): p. 29-34.
47. *National coordinating council for medication error reporting and prevention [www.nccmerp.org] - about medication errors*. [cited 2011 08.04]; Available from: http://www.nccmerp.org/aboutMedErrors.html.
48. *U.S. Food and Drug Administration - Medication Errors*. 08.03.2010 [cited 2011 08.04]; Available from: http://www.fda.gov/drugs/drugsafety/medicationerrors/default.htm.
49. Christiaans-Dingelhoff, I., M. Smits, L. Zwaan, S. Lubberding, G. van der Wal, and C. Wagner, *To what extent are adverse events found in patient records reported by patients and*

healthcare professionals via complaints, claims and incident reports? BMC Health Serv Res, 2011. **11**: p. 49.
50. *Determining the Barriers to Medication Error Reporting and Assessing Patient Safety Culture in MA Nursing Homes Instructions/Definitions for Part I.* [cited 2011 08.04]; Available from: http://www.mass.gov/Eeohhs2/docs/dph/quality/boards/nursing_patient_safety_survey_data.pdf.
51. Barber, N.D., D.P. Alldred, D.K. Raynor, R. Dickinson, S. Garfield, B. Jesson, et al., *Care homes' use of medicines study: prevalence, causes and potential harm of medication errors in care homes for older people.* Qual Saf Health Care, 2009. **18**(5): p. 341-6.
52. Kucukarslan, S.N., M. Peters, M. Mlynarek, and D.A. Nafziger, *Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units.* Arch Intern Med, 2003. **163**(17): p. 2014-8.
53. Brown, J.N., C.L. Barnes, B. Beasley, R. Cisneros, M. Pound, and C. Herring, *Effect of pharmacists on medication errors in an emergency department.* Am J Health Syst Pharm, 2008. **65**(4): p. 330-3.
54. Kaboli, P.J., A.B. Hoth, B.J. McClimon, and J.L. Schnipper, *Clinical pharmacists and inpatient medical care: a systematic review.* Arch Intern Med, 2006. **166**(9): p. 955-64.
55. Murray, M.D., J. Young, S. Hoke, W. Tu, M. Weiner, D. Morrow, et al., *Pharmacist intervention to improve medication adherence in heart failure: a randomized trial.* Ann Intern Med, 2007. **146**(10): p. 714-25.
56. *Royal pharmaceutic society of Great Britain - Guidance on Recording Interventions*. 2006 [cited 2011 22.04]; Available from: http://www.hampshirelpc.org.uk/uploads/recinterventionsguid.pdf
57. *Nationsl Patient Safety Agency [www.npsa.nhs.uk]- Safety in doses: Medication safety incidents in the NHS*. 2007 [cited 2011 08.04]; Available from: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=61392.
58. Gurwitz, J.H., T.S. Field, L.R. Harrold, J. Rothschild, K. Debellis, A.C. Seger, et al., *Incidence and preventability of adverse drug events among older persons in the ambulatory setting.* JAMA, 2003. **289**(9): p. 1107-16.
59. *Scottish Patient Safety Alliance [http://www.patientsafetyalliance.scot.nhs.uk] - Medicines Management Driver Diagram and Change Package*. [cited 2011 08.04]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/docs/presentations/MedicinesManagementDriverDiagram.pdf.
60. Stewart, C.J., L. Henderson, and L. Marson, *Cytomegalovirus - An Increasing Challenge in the Face of Changing Immunosuppression? Presentation at Edinburgh Transplant Unit Event Jan 2010*.
61. *Edinburgh Renal Unit [www.edren.org] - Transplant Handbook, CMV - Valganciclovir*. 03.12.2009 [cited 2011 13.04]; Available from: http://www.edren.org/pages/handbooks/transplant-handbook/cmv.php.
62. *Edinburgh Renal Unit[www.edren.org] - Immunosuppression protocol - October 2009 Edinburgh, Inverness, Aberdeen, Dundee, FIFE - CMV Prophylaxis*. 25.01.2011 [cited 2011 13.04]; Available from: http://www.edren.org/pages/handbooks/transplant-handbook/immunosuppression.php?searchresult=1&sstring=CMV#wb_43.
63. Moranville, M.P. and H.R. Jennings, *Implications of using modification of diet in renal disease versus Cockcroft-Gault equations for renal dosing adjustments.* Am J Health Syst Pharm, 2009. **66**(2): p. 154-61.

8 Appendices

1 – Project protocol

2 – Ethics approval

3 – Interview questions

4 - Interviews

5 – Guidelines

6 – Clinic form

7 – Questionnaire

8 – Pharmacist checklist

9 – Power-point presentation

Appendix 1

Project protocol

Title

Evaluation of antiviral prophylaxis of cytomegalovirus in patients receiving liver, kidney or pancreas transplantation

Investigator:	Sara Ann Dyrhaug, Master of Pharmacy students, University of Tromso
Clinical supervisors:	Katherine Davidson, Clinical Pharmacist RIE Scott Garden, Lead Pharmacist RIE
Academic supervisors:	Moira Kinnear, Head of Pharmacy Education, Research and Development (ERD) and lecturer in Clinical Practice, University of Strathclyde
Collaborators:	Staff participating

Introduction

Compared to international standards NHS Scotland provides overall good safety to patients, however, as for any organization, there are still errors happening that can be reduced. That is why The Scottish Patient Safety Alliance was developed[1]. This organisation co-ordinates the Scottish Patient Safety Programme(SPSP) which aims to improve the safety of hospital care. To achieve this evidence-based tools and techniques are used[2]. A similar safety initiative was initiated in 3000 hospitals in the U.S and this has saved approximately 122,00(lives.[3] Research shows that one in ten patients experience adverse events and 50% of these events are most likely avoidable. [1]

"An adverse event is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it." [4] Under the term adverse event belongs the term adverse drug event, which means "harm caused by a drug or the inappropriate use of a drug" [4]. This can easily be confused with adverse drug reaction, which actually is "Harm directly caused by a drug at normal dose". [4] To avoid adverse drug events which actually cause harm, medications errors defined as "Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer" also need to be eliminated.[5] Medication errors are the most common type of medical error happening in facilities[6] Reducing medication errors will therefore be important to improve patient safety, and to this project.

To eliminate medication errors you first have to identify where they happen. Reporting systems for healthcare is one way of identifying that. Unfortunately, most healthcare professionals will not report errors, and most medication errors, will not be reported.[7] A survey conducted on staff at a nursing home shows that important barriers for them to report errors are: fear of being blamed, lack of recognition that a medication error has occurred and fear of disciplinary action.[8] NHS uses a reporting system called Datix. It helps to manage the administration and recording of incidents, complaints and claims. [9]

Why is it important to reduce medication errors?

In addition to the obvious reasons in reducing harm and saving lives, elimination of medication errors can save NHS a lot of money. The National Patient Safety Agency (NPSA) believes that more than £750 million is used each year in England on preventable harm from medicines.[10]

Medicines associated with medication errors have been the focus of many SPSP initiatives such as anticoagulants and insulin. There are many other groups of medicines with potential for optimisation of prescribing to avoid medication errors and harm.[11] One of these groups is cytomegalovirus (CMV) prophylaxis given patients who have received an organ transplant. In immune compromised patients it is essential that CMV infection is prevented without toxic effects from the drugs. This project aims to map the processes for prescribing and administration of valganciclovir in patients who have received liver, kidney or pancreas transplantation with the intention of making recommendations to improve the use of this agent.

Cytomegalovirus and treatment

Cytomegalovirus(CMV) belongs to the herpesviruses-family. Once a person is infected with CMV, he will always have CMV in his body. Most of the time the virus will be inactive, but it can reactivate and cause illness(CMV-disease). CMV is for most people harmless, but for immune compromised patients, for example people on immunosuppressant drugs, it can be deadly.[12] An organ transplantation with a CMV-positive donor causes a CMV-negative recipient to become CMV positive. Transplant patients who are either CMV positive themselves or receive organ from a CMV positive donor are treated prophylactically against CMV. Ganciclovir and valganciclovir are still the best medical agent both for prophylactic and treatment of CMV disease, even though they are expensive and toxic. Foscarnet and cidofovir, are less used alternatives because of renal toxicity.[13]

Valganciclovir is absorbed from the gastrointestinal tract and quickly metabolised to ganciclovir. Both are antiviral drugs indicated for prophylaxis for CMV. For Solid organ transplanted patients, the dose should 900 mg once a day, starting within 10 days after transplantation and the treatment should last until 100 days post-transplantation(200 days for kidney-transplanted). Most of the drug is eliminated through renal excretion and the elimination is an important factor for interactions with other drugs.[14] Ciclosporin and Tacrolimus which are used as immune suppressants in transplanted patients can impair kidney function.[15, 16] placing patients at risk of toxicity from renal excreted medicines. Mycophenolate mofetil competes with galganciclovir for tubular secretion and may increase concentrations of both substances.[17] Both of these types of interactions can lead to excessive exposure of ganciclovir and may be associated with life-threatening adverse reactions. Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been associated with use of Valganciclovir. Therefore patients with renal impairment have to have the dose adjusted according to renal function estimated by measurement of creatinine clearance.[14]

The guidelines used for Valganciclovir at the Royal Infirmary of Edinburgh's transplant ward, is published by The British Transplantation Society "Guidelines for the prevention and management of cytomegalovirusdisease after solid organ transplantation". [18] The guidelines are designed to minimise the potential for harm caused by Valganciclovir, but there is concern that in practice such guidelines are not closely followed.

Developing good guidelines does not guarantee their use in practice. Reviews of methods for changing healthcare behaviours, indicates that mailing guidelines to targeted healthcare and publishing them does not lead to changes in staff behaviour. Dissemination and implementation of clinical guidelines requires time, passion, and resources.[19]

This project will explore processes in practice and make recommendations for change which should led to improved patient safety.

Aim

Critically review and evaluate the processes in the prescribing and administration of valganciclovir for cytomegalovirus prophylaxis in liver, kidney or pancreas transplantation.

Objectives

1. Define the processes for prescribing, administering and monitoring of valganciclovir use for CMV prophylaxis.
2. Characterise the procedures available to support decisions in the use of valganciclovir.
3. Characterise the harm assessment based on data from audit
4. Investigate problems in the prescribing, administering and monitoring of valganciclovir by interviews with clinical staff.
5. Characterise pharmaceutical care issues from prospective audit of pharmacists' contributions.
6. Critically evaluate opportunities for quality improvement by presentation of findings to an expert group.

Subjects and Settings

The project will take place on the transplant ward at the Royal Infirmary of Edinburgh. The ward has beds for 20 patients additionally there are 4 high-dependency beds. There is one team for kidney transplantation, and one for liver. The kidney- team also covers pancreas transplantations, but there are few of those. The teams consist of a junior grade doctor, medical registrar, surgical registrar, consultant physician and consultant surgeon. The team is changed after a week.

The out-patients are followed up at the out-patient clinic. During clinic visits they are seen by 2-3 nurses, a consultant and maybe a transplant-coordinator. The clinic runs twice a week for both liver- and kidney-transplanted patients. The frequency of appointments for each patient varies depending on time since the transplantation.

Project approval

Approval to conduct the study will be sought from the multidisciplinary transplant team and senior Pharmacy managers through submission to both the Pharmacy and Transplant Quality Improvement teams. Confirmation that the project does not require research ethics approval will be sought from the scientific officer of the South-East Scotland Research Ethics Committee.

Inclusion criteria

Patient that is included in part 2 of objective 3 must fit the following inclusion criteria's:

- CMV status: CMV-positive recipient, or receive organ transplantation from a CMV-positive donor.
- Uses Valganciclovir (100 days liver, 200 days kidney)
- Been discharged either within 3/4 days ago or 3 months ago.

Methods

1. Establish current practice in the prescribing, administration and monitoring of valganciclovir

- Map the actual process for prescribing and monitoring the treatment of Valganciclovi after conversation with doctors. Both junior and senior doctors in both renal and liver should be included.
- Mapping the process of administration will be mapped by talking to both junior and senior nurses.
  The questions will be prepared in advance and they will be the same for every doctor and for every nurse. Most of the questions will be open, but some will be closed to ensure the required information is obtained. (Appendix 1)

2. Find the guidelines for prophylaxis for CMV with Valganciclovir in transplanted patients by doing a literature search. There also has to be done a literature search to confirm that the guidelines are up-to-date.

3. Characterise the harm assessment based on data from audit

- Look at adverse drug events reported in the incident reporting software Datix.

- Look at real data from a snapshot on the ward and in the clinic
  The patient charts for those that fit the inclusion criteria will be reviewed. The main-focus will be if the dose is right adjusted according to creatinine clearance, but frequency of monitoring and communication about monitoring with GP will also be checked.

4. Make a questionnaire for doctors, nurses, pharmacists and coordinators about their opinions on problems around prescribing, administering and monitoring of Valganciclovir. The questions will be prepared in advance and they will be the same for every staff member participating. Most of the questions will be open, but some closed to ensure the required information is obtained. (Appendix 2)

5. Develop a checklist for the pharmacist to fill out when they look at patients on Valganciclovir. Care issues for the checklist will be identified after looking at Datix and discussing with a pharmacist. The pharmacist will fill out this checklist for 4 weeks. (Appendix 3)

6. Findings will be presented at a scheduled meeting and areas for quality improvement agreed.

References

1. *Scottish Patient Safety Alliance [www.patientsafetyalliance.scot.nhs.uk] - About the alliance.* [cited 2011 08.04]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/about-the-alliance.
2. *Scottish patient safety alliance.* [cited 2001 07.05.2011]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/
3. *The Scottish Patient Safety Alliance [http://www.patientsafetyalliance.scot.nhs.uk/] - About the Scottish Patient Safety Programme.* [cited 2011 08.04]; Available from: http://www.patientsafetyalliance.scot.nhs.uk/programme/about.
4. Nebeker, J.R., P. Barach, and M.H. Samore, *Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting.* Ann Intern Med, 2004. **140**(10): p. 795-801.
5. *U.S. Food and Drug Administration - Medication Errors.* 08.03.2010 [cited 2011 08.04]; Available from: http://www.fda.gov/drugs/drugsafety/medicationerrors/default.htm.
6. *The Association of periOperative Registered Nurses - Pediatric medicine safety.* [cited 2011 07.05]; Available from: http://www.aorn.org/PracticeResources/AORNPositionStatements/Position_PediatricMedicationSafety/.
7. Caldwell, N.A. and D.K. Hughes, *Medication errors are NOT uncommon.* Arch Dis Child, 2001. **85**(2): p. 172.
8. *Determining the Barriers to Medication Error Reporting and Assessing Patient Safety Culture in MA Nursing Homes Instructions/Definitions for Part I.* [cited 2011 08.04]; Available from: http://www.mass.gov/Eeohhs2/docs/dph/quality/boards/nursing_patient_safety_survey_data.pdf.
9. *Datix*. Available from: http://www.datix.co.uk/
10. Centre, T.N.P. *Reducing Medication Errors*. Available from: http://www.npci.org.uk/medicines_management/safety/errors/library/5mg_rme.php.
11. *Scottish Patient Safety Alliance [http://www.patientsafetyalliance.scot.nhs.uk] - Medicines Management Driver Diagram and Change Package.* [cited 2011 08.04]; Available from:

http://www.patientsafetyalliance.scot.nhs.uk/docs/presentations/MedicinesManagementDriverDiagram.pdf.
12. *Cytomegalovirus (CMV) and Congenital CMV Infection - centers for disease control and prevention*. Available from: http://www.cdc.gov/cmv/overview.html.
13. Torres-Madriz, G. and H.W. Boucher, *Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients.* Clin Infect Dis, 2008. **47**(5): p. 702-11.
14. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Valcyte.* 18.06.2010 [cited 2011 05.03]; Available from: http://www.medicines.org.uk/EMC/medicine/9315/SPC/Valcyte+450mg+film-coated+tablets/
15. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Neoral.* 04.02.2011 [cited 2011 08.04]; Available from: http://www.medicines.org.uk/EMC/medicine/1307/SPC/Neoral+Soft+Gelatin+Capsules%2c+Neoral+Oral+Solution/.
16. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Prograf.* 05.08.2010 [cited 2011 08.04]; Available from: http://www.medicines.org.uk/EMC/medicine/11102/SPC/Prograf+0.5mg%2c+1mg%2c+5mg+Hard+Capsules/.
17. *The electronic Medicines Compendium (eMC) [www.medicines.org.uk] - SPC Cellcept.* 27.10.2009 [cited 2011 08.04]; Available from: http://www.medicines.org.uk/EMC/medicine/1679/SPC/Cellcept+250mg+Capsules/.
18. *Bristish transplant society - Guidelines for the prevention and management of cytomegalovirusdisease after solid organ transplantation.*
19. Feder, G., M. Eccles, R. Grol, C. Griffiths, and J. Grimshaw, *Clinical guidelines: using clinical guidelines.* BMJ, 1999. **318**(7185): p. 728-30.

Appendix 2

Ethics approval

South East Scotland Research Ethics Service

Waverley Gate
2-4 Waterloo Place
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EH1 3EG
Telephone 0131 536 9000

NHS Lothian

Name: Moira Kinnear
Address: Head of Pharmacy Education
Dept of Pharmacy
Western General Hospital
Edinburgh
EH4 2XU

Date: 21/12/2010
Your Ref:
Our Ref: NR/1012AB9
Enquiries to: Alex Bailey
Direct Line: 0131 465 5679
Email: alex.bailey@nhslothian.scot.nhs.uk

Dear Moira,

Full title of project Evaluation of antiviral prophylaxis of cytomegalovirus in patients receiving liver, kidney or pancreas transplantation

You have sought advice from the South East Scotland Research Ethics Service on the above project. This has been considered by the Scientific Officer and you are advised that, based on the submitted documentation (Protocol SD.doc), it does not need NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees in the UK. The advice is based on the following:

- *The project is an audit using only data obtained as part of usual care, but note the requirement for Caldicott Guardian approval for the use or transfer of person-identifiable information within or from an organisation*

- *The project is an opinion survey seeking the views of NHS staff on service delivery.*

If this project is being conducted within NHS Lothian you should inform the relevant local Quality Improvement Team(s).

This letter should not be interpreted as giving a form of ethical approval or any endorsement of the project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements. However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further. Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

You should retain a copy of this letter with your project file as evidence that you have sought advice from the South East Scotland Research Ethics Service.

Yours sincerely,

Alex Bailey
Scientific Officer
South East Scotland Research Ethics Service

Appendix 3

Interview questions

Interview; Mapping the process of prescribing and monitoring the treatment of Valganciclovir after interviewing prescribing staff.

Prescribing

What are the patient criteria for starting Valganciclovir prophylaxis (in transplant patients?)?

When during the transplant process is the treatment initiated?

Does every patient with normal kidney function get the same dose, or do other factors influence dose adjustments?

- If other factors are considered, are prescribers supported through some form of guidelines or is it entirely independent clinical judgement?

How do you decide the dose for a person with renal impairment?

Which formula do you use to calculate Creatinine clearance?

Do you use eGFR for informing your prescribing decisions?

Do you ever use valganciclovir oral solution?

- If yes, in which cases?

What is the treatment duration? For how long is valganciclovir prescribed?

Monitoring

When monitoring: Which lab tests are done and how often?

- Does the frequency of monitoring change after adjusting doses?

How do you adjust the dose according to Creatinine clearance in renal impaired patients? (When do you decide to lower the dose and by how much?)

- Do you use literature such as for example BNF or guidelines, or do you just use your memory?

Do you follow any guidelines?

- if so which one and do you follow accurately or do you deviate?
- Do you have specific reasons for this?

Do you communicate with the GP and expect them to participate in monitoring this therapy?

- How is this communication documented?

If you identify a prescribing-error or instances where the treatment is not optimised, what do you do and how do you document this?

Interview; Mapping the process of administrating Valganciclovir after interviewing nurses.

How are nurses made aware of new prescriptions? Is the nurse notified? Or do they have to check the kardex?

Are all pharmacy orders from nurses?

- If no, who does it?

- How are the orders documented at the ward?

What is the process of drug administration ?

- Are any measures initiated to improve medicine safety in administration?

Are you aware of the precautions required for handling this medicine (valganciclovir)?

If an administration error happens, who is notified, and where is it documented?

Appendix 4

Interview transcript

Mapping the process of prescribing and monitoring the treatment of Valganciclovir, after interviewing prescribing staff.

Interview with liver senior doctor:

Prescribing:

What are the patient criteria for starting Valganciclovir prophylaxis (in transplant patients)?

We have two different criteria, one for liver and one for kidney/pancreas. The criteria for the liver side are CMV-positive to CMV-negative recipient or in re-transplants.

For renal/pancreas: anyone who is either donor (CMV)-positive and recipient (CMV)-negative or recipient positive regardless of donor-status. So it's slightly wider.

When during the transplant process is the Valganciclovir treatment initiated?

It is written up immediately after transplantation, they might not get it immediately after because they might be in intensive care and they are not providing oral medicines. It doesn't need to be gives the 2 first days, but it is written up on the first, or should be written up on the 2 first days

Does every patient with normal kidney function get the same dose, or do other factors influence dose adjustments?

It is on the Cockcroft-Gault, so it should be renal function. We have changed dose depending on marrow suppression, but that is not at the time of initial prescription.

- **If other factors are considered, are prescribers supported through some form of guidelines or is it entirely independent clinical judgement?**

  At the time of prescription It is solely based on Cockcroft-Gault. I don't remember us modifying anyone right at the outset. We have further down the line, but at the initial prescription it's the Cockcroft-Gault. Whether we get it right is a different matter.

How do you decide the dose for a person with renal impairment?

(This question was not asked because it was already answered)

Which formula do you use to calculate Creatinine clearance?

(This question was not asked because it was already answered)

Do you use eGFR for informing your prescribing decisions on Valganciclovir?

No! I use the pharmacist (laughs) I e-mail her regularly for her to tell me the correct dose

Do you ever use valganciclovir oral solution?

- If yes, In which cases? The answer is I don't know. I don't know if any patients have been put on it.

What is the prophylaxis treatment duration?

For liver: 3 months after transplant or an episode of acute rejection

For kidney: 6 months

Monitoring

When monitoring: Which lab tests are done and how often?

Urea Creatinine and full blood count are done when they come to clinic. How often depends on the clinical condition, and duration from transplant, Initially at least weekly, after a month it is down to forth nightly and by three months it is probably been three weeks. Since they've been seen. They are not brought back for CMV monitoring as such, but for clinical reasons.

- **Does the frequency of monitoring change after adjusting doses?**

  No, well usually for the liver side if we have adjusted the dose I suppose there are one in two conditions that have happened. One is that they have had renal dysfunction which has gotten better and therefore their prophylactic dose has been increased, in other words they are well. So therefore the periods between monitoring tends to be extended.

  And then there is the group who have progressed renal dysfunction post-transplant period who will be coming back ever more frequently as their kidneys appear to get worse. So their frequency of monitoring will automatically go up, but it is not for valganciclovir monitoring.

How do you adjust the dose in renal impaired patients?

I email my transplant pharmacist and provide the information needed to work out the Cockcroft-Gault and then he/she tells me the answer. I don't try to do it myself (laughs).

- **Would you change the dose if it wasn't optimal according to blood tests at one occasion? Or do you wait to see if there is a trend?**

  I would tend to adjust it after the level that they are at. The worrying being that when you see them in the clinic if they come in with a worsening renal function, then that is going to continue for a while. You are probably not going to see them for another week. To be honest there has usually been a trend anyway before. You have already seen a trend in the previous dose level, and then are moving to another dose level. So you probably already seen that trend.

- **Do you use literature such as for example BNF or guidelines, or do you just use your memory when adjusting doses?**

  (This question was not asked because he/she already answered that he uses the pharmacist.)

In general, do you follow any guidelines when prescribing and monitoring Valganciclovir?

The guidelines from The British Transplant Society.

- **if so which one and do you follow accurately or do you deviate?**

  (laughs)They are guidelines, they are not rules. They inform decisions. They are guidelines, they are not mandatory. We have had patients who are CMV-positive to negative transplant but have become profoundly leucopenic, and we have stopped Valganciclovir early. So that would not necessary be in the guidelines but done for clinical reasons.

- **Do you have specific reasons for this?**

  (This question was not asked because it was already answered)

Do you communicate with the GP and expect them to participate in monitoring this therapy?

No, we don't expect them to monitor themselves. Maybe ask patients to attend their practise to have full blood count and renal function checked, but we get the results and we make the decisions. So they are involved it is as far as participating with taking blood tests, but we don't expect them to make important decisions.

- **How is this communication documented?**

  In clinical letters, they probably will go out a while after they have had their blood test because of secretary delays. But the co-ordinators and the patients they all know. For most practises the GP (noise).

If you identify a prescribing-error or instances where the treatment is not optimised, what do you do, and how and where do you document this?

Correct the error, make sure they are on the right dose, right treatment, you correct what is wrong. It gets documented in letters. For the liver side to be honest we don't discuss it at a m&m (morbidity and mortality) meeting.

Interview with liver senior doctor

Prescribing

What are the patient criteria for starting Valganciclovir prophylaxis (in transplant patients)?

We prescribe valganciclovir prophylaxis in two situations, one is a patient who receives a graft that is positive for CMV and they themselves are CMV-negative, so they will get a three months prophylaxis with valganciclovir. And all re-transplants gets valganciclovir, people who have had a liver transplant before and have a new transplant, not in the same episode. They should at least get valganciclovir for three months minimum.

When during the transplant process is the Valganciclovir treatment initiated?

The prophylaxis is started at day 7.

Does every patient with normal kidney function get the same dose, or do other factors influence dose adjustments?

I think they get the same dose if the kidneys are okay. They should get 900 mg

- **If other factors are considered, are prescribers supported through some form of guidelines or is it entirely independent clinical judgement?**

  (This question was not asked because already answered no other factors were included.)

How do you decide the dose for a person with renal impairment?

We usually speak to the pharmacist. we get this discussion because the company (Roche) who make Valganciclovir they always tell us that it is based on Cockcroft-Gault which is not what we use or eGFR for renal function. So that's what their data is based on, So we depend a bit on the pharmacist to tell us what the Cockcroft-Gault give. Cause the number that we get up there is not Cockcroft-Gault. Estimation of eGFR.

As far as I can remember if they got normal kidney-function it is greater than 60 ml/min then they get 900 mg. If it's 40 -60 ml/min its 450 mg. And less than that then we have alternate things. So we do depend a bit on the pharmacist on help on that regard, but we are aware that if the kidneys aren't working properly then we need to reduce the dose. I suspect we are reasonable at that, the problems that we have had is when the kidneys get better and we have not gone back up to the dose. We have had 1or 2 problems with CMV when we have not increased the dose appropriately.

Which formula do you use to calculate Creatinine clearance?

(This question was not asked because it was already answered)

Do you use eGFR for informing your prescribing decisions on Valganciclovir?

(This question was not asked because it was already answered)

Do you ever use valganciclovir oral solution?

- **If yes, In which cases?**

Not to my knowledge. I am aware that it is there, but I haven't used it yet.

What is the treatment duration?

(This question was not asked because it was already answered)

Monitoring

When monitoring: Which lab tests are done and how often?

CMV-DNA is what we ask for. How often probably varies from individual to individual. If they are in prophylaxis I certainly don't do CMV-DNA unless they have symptoms. If they stop prophylaxis after three months I would for the two next visits do CMV-DNA. Cause that is often were we see CMV-disease, when they stop prophylaxis. And we tend to do CMV testing in patients who are not on prophylaxis who have an unknown illness or unexplained changes in their liver function tests around and after the first six weeks. I'm not sure if there is anything written down that tells us what we should do.

- **Does the frequency of monitoring change after adjusting doses?**

  Does it? Probably.. possibly

How do you adjust the dose in renal impaired patients?

If CrCl reduces below 60 then we drop from 900 to 450 mg daily. And if it's less than 40, 25-40 it is 450 mg alternate days, and if it's less than that I think it is twice a week.

- **Would you change the dose if it wasn't optimal according to blood tests at one occasion? Or do you wait to see if there is a trend?**

  Personally I think you should wait and see if there is a trend

- **Do you use literature such as for example BNF or guidelines, or do you just use your memory when adjusting doses?**

  I usually use the pharmacist. There is a kind of poster that gives us the information from the company. I don't often use the BNF.

In general, Do you follow any guidelines when prescribing and monitoring Valganciclovir?

The guidelines that we follow is our own protocol, which we discuss every year, and I am aware that the renal physician have changed their prophylaxis from three months to six on the basis of a recent study. We haven't adopted that yet, and I am not aware of any liver transplant guidelines who have suggested we should. In my own opinion there are patients who I think we should be given six month prophylactic treatment. These are the younger patients who require a lot of immuno suppression who are Donor-positive/ recipient-negative.

- **If so which one and do you follow accurately or do you deviate?**

  I usually deviate

- **Do you have specific reasons for this?**

  Well yes (laughs), from my own past experience. There have been patients were we stop after three months and they get CMV-disease and become quite unwell for a time. So there are patients were I have chosen to keep them on prophylaxis for a little bit longer than three months.

Do you communicate with the GP and expect them to participate in monitoring this therapy?

We do communicate with them, but don't really expect them to participate in the monitoring because if you ask them to do CMV-DNA that never happens. So we don't expect them to do viral-loads. We ask them on occasions to check kidney function and see if there has been any change.

- **How is this communication documented?**

  Hopefully, (laughs)

If you identify a prescribing-error or instances where the treatment is not optimised, what do you do, and how and where do you document this?

That's a good question. If I was being honest, which I should I would only document it in a written letter within the notes. I wouldn't do anything more.

Interview with liver junior doctor

Prescribing

What are the patient criteria for starting Valganciclovir prophylaxis (in transplant patients)?

I think.. (pause) If it is a CMV-positive donor with a negative recipient, or the recipient is CMV-positive.

When during the transplant process is the Valganciclovir treatment initiated?

I don't know (laughs). I have no idea. A day afterwards? I'm not entirely sure.. (pause) If with Valgan, that's oral, so it as to be when they are kinda alert and awaken enough to take it, but I don't know (laughs).

Does every patient with normal kidney function get the same dose, or do other factors influence dose adjustments?

Well I know Creatinine clearance comes in to it, but I'm not sure what else is involved in adjusting the dose.. weight maybe? (pause) Not sure.

- **If other factors are considered, are prescribers supported through some form of guidelines or is it entirely independent clinical judgement?**

  (This question was not asked because he/she did not know about any other factors.)

How do you decide the dose for a person with renal impairment?

You ask a pharmacist to work it out(laughs) I think it's based on creatinine clearance, but I'm not entirely sure, and it its different if they are dialysed or on a filter. It's a different dose regiment.

Which formula do you use to calculate Creatinine clearance?

It should be the Cockcroft-Gault formula for creatinine clearance, not the eGFR from the list

Do you use eGFR for informing your prescribing decisions on Valganciclovir?

No

Do you ever use valganciclovir oral solution?

- **If yes, In which cases?**

I have never used it, it as always been the tablets.

What is the treatment duration?

I don't know (laughs). I have no idea.

Monitoring

When monitoring: Which lab tests are done and how often?

I don't know, I presume that they should be monitoring renal function and then dose adjust. And they need to keep an eye on the full blood count. I don't know if it is as bad with valganciclovir as with for example foscarnet. I'm not entirely sure. I have no idea how often they do that. When they are in-patients they are done every day, but I don't know what happens when they go home.

- **Does the frequency of monitoring change after adjusting doses?**

  (This question was not asked because he/she already answered that she did not know the frequency)

How do you adjust the dose in renal impaired patients?

There is a little table that you use. It is on our wall in the doctors' room. It tells you what to give. So I just look at that.

- **Would you change the dose if it wasn't optimal according to blood tests at one occasion? Or do you wait to see if there is a trend?**

  (This question was not asked because he/she had said in the interview to the parallel project conducted earlier that he/she did not go to clinic.)

- **Do you use literature such as for example BNF or guidelines, or do you just use your memory when adjusting doses?**

  (This question was not asked because he/she had said in the interview to the parallel project conducted earlier that he/she did not go to clinic.)

In general, Do you follow any guidelines when prescribing and monitoring Valganciclovir?

I don't know. I'm not sure (laughs).

- **if so which one and do you follow accurately or do you deviate?**

  (This question was not asked because he/she answered that he/she did not know if he/she used any guidelines.)

- **Do you have specific reasons for this?**

  (This question was not asked because he/she answered that he/she did not know if he/she used any guidelines.)

Do you communicate with the GP and expect them to participate in monitoring this therapy?

I have never sent anyone home on it. In this week (laughs). So I'm not sure. I don't know whether they monitor it. I imagine they would, and you would have to speak to them..(pause) I think they would have to agree to do that. I have not had to do that, so I'm not sure.

- **How is this communication documented?**

  (This question was not asked because he/she did not know if he/she should communicate with the GP.)

If you identify a prescribing-error or instances where the treatment is not optimised, what do you do, and how and where do you document this?

If there is an error with the prescription I would make sure the right thing is prescribed, and what was wrong is crossed of. I suppose you should fill out an incident report about it, cause there have been an error. And you should let the senior doctors know that there has been given incorrectly or prescribed incorrectly. I would probably let the nurse in charge know what happened cause they probably got their own incident reports to fill out.

Interview with renal senior doctor

Prescribing

What are the patient criteria for starting Valganciclovir prophylaxis (in transplant patients)?

At the moment for renal and sometimes renal/pancreas transplants all patient except D-/R- will get valganciclovir.

When during the transplant process is the Valganciclovir prophylaxis treatment initiated?

It is usually initiated at day 1. It is often written up as they start, when they are called in and have their first initially kardex is written, sometimes it is delayed to day 1, cause there might be some misinformation about the viral status. Anything later than that that is a problem. It is certainly picked up before they go home.

Does every patient with normal kidney function get the same dose, or do other factors influence dose adjustments?

None of our patients have normal kidney function. So, all prescriptions are based on Cockcroft-Gault creatinine clearance. There will be occasions where patients have neutropenia that might mean that they come off Valganciclovir early or have a reduced dose or something else.

- **If other factors are considered, are prescribers supported through some form of guidelines or is it entirely independent clinical judgement?**

  (This question was not asked because he/she did not answer any other factors.)

How do you decide the dose for a person with renal impairment?

(This question was not asked because it was already answered)

Which formula do you use to calculate Creatinine clearance?

(This question was not asked because it was already answered)

Do you use eGFR for informing your prescribing decisions on Valganciclovir?

No

Do you ever use valganciclovir oral solution?

- **If yes, In which cases?**

  I haven't yet, but I know it is available for people with Cockcroft-Gault creatinine clearance less than 10 ml/min. There are patients who don't like swallowing tablets and we would use it in that situation, but I have not personally had a patient in that situation.

What is the treatment duration?

At the moment we do six months or 200 days.

Monitoring

When monitoring: Which lab tests are done and how often?

Monitoring renal function. It depends, some patients we monitor..we look for CMV-PCR depending on status. If they were recipient (CMV) negative and there was a clinical suspicion of a CMV infection we would check for that, but that is not routinely monitored in patients on prophylaxis. White blood cell counts is important. And there might be dose adjustments or early sesation on valganciclovir in case of neutropenia. The other monitoring liver function test goes on anyways.

- **Does the frequency of monitoring change after adjusting doses?**

(This question was not asked)

How do you adjust the dose in renal impaired patients?

Depending on their Cockcroft-Gault creatinine clearance.

- **Would you change the dose if it wasn't optimal according to blood tests at one occasion? Or do you wait to see if there is a trend?**

  It depends. In varying occasions if you see patient who is right on the edge of moving into the next group and then you are not going to see them again for the next couple of weeks then I would. It is easier for them to get it sorted out then and there.

Usually that is because you know if you see them on the morning, you know that they will not get the creatinine back before this evening. So when looking at the trend, I'm predicting that their CrCl will push them into the next group. So I can tell them to increase the dose, and at evening when the results comes back I phone them and say:"No, actually don't, stick to the original dose you were on".

- **Do you use literature such as for example BNF or guidelines, or do you just use your memory when adjusting doses?**

  We got big post-its stuck on the OPD (out-patient department?) But we use Cockcroft-Gault to find CrCl.

In general, Do you follow any guidelines when prescribing and monitoring Valganciclovir?

We use the guidelines based on Cockcroft-Gault.

- **If so which one and do you follow accurately or do you deviate?**

  You might call it deviate if you predict CrCl, but I would call it pre-emptily treating. Our previous orders would suggest that the most likely risk is lagging behind, so we have to make sure the prescription matches the level of function.

- **Do you have specific reasons for this?**

  (This question was not asked)

Do you communicate with the GP and expect them to participate in monitoring this therapy?

No, not really because we see the patients so frequently at the clinic in the first time. So to ask the GP to take on additionally monitoring would most likely only complicate matters.

- **How is this communication documented?**

(This question was not asked because he/she did not answer that he/she communicated with the GP.)

If you identify a prescribing-error or instances where the treatment is not optimised, what do you do, and how and where do you document this?

If it is a prescribing error in that a patient is on a certain dose of valganciclovir and the blood results come back and show that the creatinine has dropped and the patients is getting to much valganciclovir that's not necessarily a prescribing error it's just that their function has changed and you need to adjust either up or down. So if someone has failed to recognised improving function and make a change, I would change the prescription. I certainly don't Datix® that sort of things. Cause I think Datix® would just get bumped down (laughs), cause there is to many examples of that. You can argue that it should be.

Interview with renal middle grade doctor

Prescribing

What are the patient criteria for starting valganciclovir prophylaxis in transplant patients?

In this unit then all other than CMV-negative donor and CMV-negative recipient is the only patient group that isn't routinely started on valganciclovir.

When during the transplant process is the valganciclovir treatment initiated? Immediately.

- **Immediately after the transplant?**

  Yes

Does every patient with normal kidney function get the same dose, or do other factors influence dose adjustments?

There is a protocol on our webpage (edren.org) which we follow based on the patients weight and CrCl, which tells us the exact regiment for Valganciclovir

- **If other factors are considered, are prescribers supported through some form of guidelines or is it entirely independent clinical judgement?**

  (This question was not asked because it was already answered)

How do you decide the dose for a person with renal impairment?

By consulting the algorithm.

Which formula do you use to calculate creatinine clearance?

Cockcroft- Gault

Do you use eGFR for informing your prescribing decisions?

For Valganciclovir, No!

Do you ever use valganciclovir oral solution?

Yes

- **If yes, In which cases?**

  If the patient is unable to take tablets but able to take the solution.

What is the treatment duration? For how long is valganciclovir prescribed?

Routinely, it would be for 180 days

Monitoring

When monitoring: Which lab tests are done and how often?

The patient can get CMV-PCR, and it tends to varies how often depending on the clinical situation.

- **Does the frequency of monitoring change after adjusting doses?**

The frequency of monitoring will be change more with the clinical picture rather than change in dose of the Valganciclovir

How do you adjust the dose according to creatinine clearance in renal impaired patient?

- **Would you change the dose if it wasn't optimal according to blood tests at one occasion? Or do you wait to see if there is a trend?**

  (This question was added after this interview)

- **Do you use literature such as for example BNF or guidelines, or do you just use your memory?**

  I would use edren.org

D**o you follow any guidelines?**

Yes, guidelines on edren.org

- **if so which one and do you follow accurately or do you deviate?**

  Accurately

- **Do you have specific reasons for this?**

  (This questions was not asked)

Do you communicate with the GP and expect them to participate in monitoring this therapy?

I think normally CMV we will check here at the transplant clinic rather than to get the GP to check.

- **How is this communication documented?**

  That's probably unclear

If you identify a prescribing-error or instances where the treatment is not optimised, what do you do and how do you document this?

You aim to address the problem. You document accurately what's happened, and what you are going to do about it and you communicate either verbally or in writing depending on the urgency on the situation with the relevant people involved. The aim being to correct it for that patient and minimizing the likelihood of a similar error happen on other patients.

Interview with renal Junior doctor

Prescribing

What are the patient criteria for starting Valganciclovir prophylaxis in transplant patients?

As far as I am aware it is either patient who are CMV-positive before starting immune suppression or receiving organ from a CMV-positive donor.

When during the transplant process is the treatment initiated?

The day after the transplant

Does every patient with normal kidney function get the same dose, or do other factors influence dose adjustments?

Essentially we start with Valganciclovir (noise) mg three times a week when the patient gets a new kidney. And then as the patients renal functions improves and recovers over a period of days, the frequency of the dose increases. So it depends on the renal function, and usually Valganciclovir require a steady dose increase as the graft starts to work

- **If other factors are considered, are prescribers supported through some form of guidelines or is it entirely independent clinical judgement?**

We got a website with a protocol that tells us exactly what to do. www.edren.org

How do you decide the dose for a person with renal impairment?

You calculate their eGFR by using their weight, age and their CrCl

Which formula do you use to calculate creatinine clearance?

I think we use the Cockcroft-Gault equation, I can't remember.

Do you use eGFR for informing your prescribing decisions?

(Did not ask that question since he/she already said he/she used is above)

Do you ever use valganciclovir oral solution?

- **If yes, In which cases?**

  No tablets.

What is the treatment duration? For how long is valganciclovir prescribed?

I think it's lifelong in CMV positive patients, I'm not sure.

Monitoring

When monitoring: Which lab tests are done and how often?

For CMV reactivation we do a CMV PCR, So thats a PCR to determine the numbers of copies of CMV pr ml blood, and how often that's done varies on the patient. For the patients that are unwell or are known to have reactivation it's done maybe twice a week, and for the patients that haven't had any problems with reactivation maybe done every few month or every sixth month. We would certainly have it done in every CMV-positive patient that becomes unwell.

- **Does the frequency of monitoring change after adjusting doses?**

I don't think so.

How do you adjust the dose according to creatinine clearance in renal impaired patients?

- **Would you change the dose if it wasn't optimal according to blood tests at one occasion? Or do you wait to see if there is a trend?**

  (This question was added after this interview)

- **Do you use literature such as for example BNF or guidelines, or do you just use your memory?**

  We would use our protocol on our website.

Do you follow any guidelines?

Yes I do what the pharmacist tells me most of the time(laughs)

- **if so which one and do you follow accurately or do you deviate?**

  I follow what the pharmacist tells me(laughs)

- **Do you have specific reasons for this?**

  (This questions was not asked)

Do you communicate with the GP and expect them to participate in monitoring this therapy?

No. We will communicate with the GP and tell them which drugs they are on, but I'm not sure that we would expect them to participate in the monitoring.

- **How is this communication documented?**

  (This question was not asked)

If you identify a prescribing-error or instances where the treatment is not optimised, what do you do and how do you document this?

With a prescribing-error you would correct it, and you write in the notes what have happened.

And if there is any detriment to the patient you would tell the patient at the same time, so they're informed that there has been an error. Also I would make sure that all the doctors looking after the patient knew and the consultant was aware. And that's probably all I would do.

Interview; Mapping the process of administrating Valganciclovir after interviewing nurses.

Interview with senior nurse

How are nurses made aware of new prescriptions? Is the nurse notified? Or do they have to check the kardex?

As in if something is prescribes for the patient. The doctors always come and hand it you. 99 % of the time. And let you know what this patient needs whatever at whatever time.

Who orders from pharmacy? (Only nurses? All nurses?)

Orders for individual patients are done by the trained nurses. Also sometimes the pharmacist is checking things, and if he/she sees that you know [name] needs Paracetamol and he/she'll order it for him. [The pharmacist] will do that and get you to sign it off (pause). The registered nurses do the ordering for the pharmacy as well. For our stocks and cupboards. So the nurses you know do all (pause) mostly.

- **How are the orders documented at the ward?**

  We have a sheet. It's like a form with two weeks sheet.

  And every now and then the pharmacists will come up to the ward and maybe re-amp your cupboards and see in the cupboard what we have been using a lot of, and what have been stopped. Cause drugs change all the time. So we tend to re-amp the

cupboard every now and then, and then the stocks reflect your sheets.(pause) So it's a pharmacy order form that we do twice a week. And on it you got your drugs and how many we think we need to top up of the Paracetamol...Ten boxes of Prednisolon or whatever..And there is a guide as to what they think you should have as a minimum order.. so maybe ten boxes of MMF. Ten boxes of Tacro. 15 of Paracetamol.

What is the process of drug administration? (How does the drug rounds happen?)

Well.. I suppose you have seen these tabards that we now have to wear.

Years ago we had a lovely big drug trolley, that we invested a lot of time and effort into nurses backs. And everything was at your level and you went round and everybody knew you were on a drug round so they knew not to bother you cause you had a big trolley of drugs in front of you. And you would basically dispense at this nice high table, and before we moved to the new hospital we got the POD-system? Every patient has a locker with their drugs in. And of course the patient locker has to be in a certain level, with years a bunch of them have been broken. The majority of the drugs you dispense..all the drugs you dispense is in the patient's locker. And nobody knows you are on a drug round, cause they can't see you.so there is a lot of interruption. Mistakes in general over the years have escalated. So we got these lovely tabards that we now wear, so that people know not to speak to us cause obviously we are on a drug round.. (pause) Which I think is wonderful because we needed to do something. But if we just bring back the old trolley we would get away from all that, plus you are back and forth to the cupboards half a dozen times to get restocks of things, and somebody else has got the cupboard key and..you know.. It took me an hour to do a whole ward of drugs years ago, now it takes me an hour and a half to do six patients.. And I am quite appalled of

how long time it takes in the morning. And that is not just the self education of patients..that is the time in itself.. but it is trying to find the key and the geographical layout of where we are..(pause) It is not ideal. And we have no base cause the patients bed tables are cluttered, the lockers are cluttered

- **Do you know about any measures initiated to improve medicine safety in administration?**

  Well, At the minute I would say we got these tabards that has been brought in the last wee while. This is to try and basically improve errors, so you are not interrupted constantly. So that's one thing. And we used to have education-coordinators who would arrange..so if you had some junior who struggled, then they could be supervised. You could be mentored slightly more. And those roles are all kind of gone. But if you worry about anyone and felt they needed a bit more information there are courses on drug administration...(Pause) There is drug administration courses that the nurses can do to try to give them a bit more confidence with lings like that.

Are you aware of the precautions required for handling this medicine(valganciclovir)?

No

If an administration error happens, who is notified, and where is it documented?

If you discover that you have made a mistake..or someone comes to you and have made a mistake the first thing you do is check the patient. And then you would let the doctors know. Nine out of 10 times you would discuss it with the patient, and let them know. And they all should be documented to medical notes

Interview with junior nurse

How are nurses made aware of new prescriptions? Is the nurse notified? Or do they have to check the kardex?

Ehm.. They are pretty good at telling us that there is a new drug on the kardex. Sometimes they do escape telling you, but you are pretty good at picking it up yourself. But the doctors tell you about 99 % of the times.

Who orders from pharmacy? (Only nurses? All nurses?)

We have like routine pharmacy, we to every two nights on night shifts were we have just out standard in the cupboards and a nurse will order that, however if we need a drug we do not stock in the ward a nurse will just order with a IPS(?) down to pharmacy. So it is only nurses who can order drugs. Or the pharmacist.

- **How are the orders documented at the ward?**

  We have our pharmacy sheet that we send down for the main stock. And for independent patients it is all in the IPS book.

What is the process of drug administration? (How does the drug rounds happen?)

We have just implemented a new system with the tabard system with these tabards that says do not interfere the nurses. And what we do is that we have two out of tree nurses doing that

at the time, and there is always a spare nurse walking about.(pause) So it's just the tabards. We try to get no one to disturb us, so that we won't make mistakes. So that system is quite good.

- **Do you know about any measures initiated to improve medicine safety in administration?**

  Tabards. Because there were a few mistakes before they were brought in, so that's why we brought them in. So that people are aware of not to speak to us when we have them on.

Are you aware of the precautions required for handling this medicine(valganciclovir)?

Yeah, you mean like using gloves and don't come in to contact with it? It is quite toxic. Also when we are finished with it we have to put it into a special sharps bin. It will be the pharmacist and the nurses who educate the patient on this.

If an administration error happens, who is notified, and where is it documented?

For errors made nurses have to document in the notes. We also have to inform the doctors. And also we have to fill out an incident report on the computer, and it gets sent to important people and it is dealt with there.

Appendix 5

Guidelines

Valganciclovir

Criteria for patient selection

For prevention of CMV disease in high risk transplant patients identified as follows:

Renal and Simultaneous kidney-pancreas transplant (SKP) - All transplant recipients except CMV –ve recipients of CMV –ve donors

Valganciclovir has replaced Ganciclovir for prevention of CMV disease. Prescriptions will be initiated in hospital within 10 days of transplantation. Therapy will be continued in primary care for up to a total of 180 days treatment for which a shared-care protocol will be provided.

The initial valganciclovir dose is dependent on renal function as shown in the table below:

Creatinine clearance (ml/min)	Prophylactic dose
>60	900mg od
40 to 59	450mg od
25 to 39	450mg every 2 days
10 to 24	450mg twice weekly
<10	100mg three times weekly after dialysis

Valganciclovir is available as 450mg tablets (pink) or as an oral solution and the brand name is Valcyte□. The tablets should be taken with food and not broken or crushed.

FBC and LFTs must be monitored daily during therapy.
Leucopenia can occur with valganciclovir treatment and this is a common

cause for discontinuing the drug prematurely.

Note: Surveillance for CMV post - transplant is not performed routinely in the Unit.

Investigation of any episode of illness which might be CMV related, at any stage following a transplant operation.

- An EDTA (9 ml or 3 x 2.5 mls sample for CMV should be sent to Virology whenever is clinically relevant. ON request form include details of illness (e.g. pyrexia or hepatitis etc.) Request CMV PCR and CMV culture. Please try to ensure samples reach Virus Lab by midday. The rapid culture may provide an answer sooner than PCR in some cases.

- It will often be appropriate to send respiratory or other samples to virology - bronchoalveolar lavage or induced sputum for investigation as usual or colon biopsies.

Edren.org – Immunosuppression protocol – October 2009 (Edinburgh, Inverness, Aberdeen, Dundee, Fife) – CMV prophylaxis

All patients receiving a kidney and/or pancreas transplant except CMV negative recipients of CMV negative grafts should receive prophylaxis with Valganciclovir (dosing according to eGFR)

Duration of prophylaxis should extend to 6 months (180 days)

Protocol for in-patient management following liver transplantation. Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh – Control of infections – Prophylaxis – Anti-viral – CMV

High risk recipients i.e. CMV negative patients receiving a CMV positive donor and all retransplants,
will receive oral valganciclovir 900mg once daily commencing at day 7 and
continue until 3 months post-transplant. (Adjusted for renal function).

Protocol for out-patient management following liver transplantation. Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh – Management of specific problems – CMV

If patient is suspected of having CMV disease send 10ml red (EDTA) tube to virology for CMV-DNA by PCR rapid culture. If appropriate can also send tissue (gastric, colonic, liver biopsy material) for CMV culture – discuss cultures beforehand with virology (Duty Virologist, REI bleep 5981). Quantitative PCR for blood CMV-DNA is also available.

If CMV disease is confirmed the treatment is IV ganciclovir 5 mg/kg/bd (reduce dose in renal failure – discuss with Pharmacist on bleep 5132). If patient is well and lives sufficiently close to the transplant unit or their referring hospital to visit twice daily, it may be possible to administer this IV course as an out patient. Alternatively, consider oral valganciclovir 900 mg twice daily instead of IV therapy

Appendix 6

Clinic form

Collecting real data from a snapshot in the clinic.

Inclusion criteria; All post-transplanted pasients on Valganciclovir prophylaxis visiting the clinic at the day of collecting data.

	Age	**weight**	**Sex**	**Creatinine**	**CrCL**	**Calculated dose**	**Given dose**	**Time since Tx**	**Frequency of labtests (approximately)**	**Communication with GP**
Pasient 1 (_____)										
Pasient 2 (_____)										
Pasient 3 (_____)										
Pasient 4 (_____)										
Pasient 5 (_____)										
Pasient 6 (_____)										
Pasient 7 (_____)										

Appendix 7
Questionnaire

Questionnaire about staff opinion about risks of errors in prescribing, administration and monitoring of Valganciclovir.

	I think there is a risk of errors that will always lead to harm	I think there is a risk of errors that might lead to harm in some cases	I think there is a risk of errors that will never lead to harm	I think there is no risk of errors (with or without harm as consequence)	Comments
Deciding if Valganciclovir should be prescribed					
Deciding when to start treatment					
Deciding dose for patients with normal kidney function					
Deciding dose for renally impaired patients					
Calculating Creatinine clearance					
Choosing correct drug formulation					
Deciding treatment duration					
Administering right drug					
Administering at right time					
Adjusting dose after measurement of Creatinine clearance					
Collaborate with GPs on treatment and monitoring					

Appendix 8

Pharmacist checklist

		Patient 1	Patient 2	Patient 3	Patient 4
	Initials				
	Sex				
	Age				
	weight				
Filled out only at the first visit	**Appropriate prescribing for CMV- status**				
visit 1	**Type of transplantation**				
Day _ since Tx	**Pharmacicst intervention**				
	1=Interaction 2=Dose increased 3=Dose decreased				

visit 2	**Creatinine**				
Day _ since Tx	**Creatinine clearance**				
	Pharmacist Intervention				

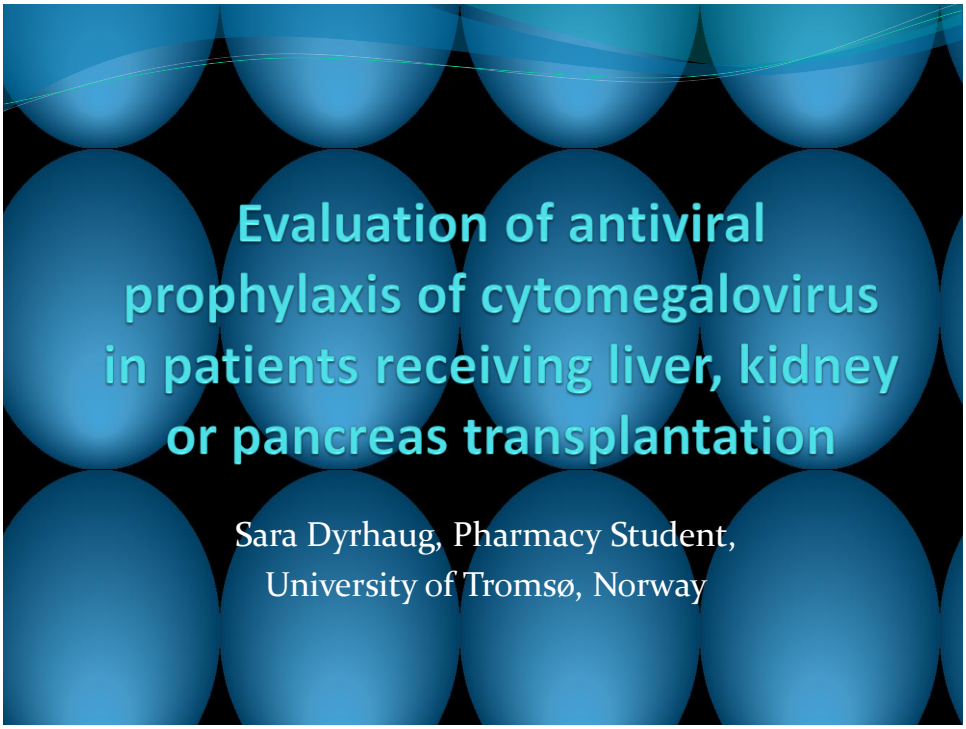
visit 3	**Creatinine**				
Day _ since Tx	**Creatinine clearance**				
	Pharmacist Intervention				

visit 4	**Creatinine**				
Day _ since Tx	**Creatinine clearance**				
	Pharmacist Intervention				

visit 5	**Creatinine**				
Day _ since Tx	**Creatinine clearance**				
	Pharmacist Intervention				

Appendix 9

Power point presentation



Supervisors and collaborators

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  Steve Hudson, Professor of Pharmaceutical Care, University of Strathclyde
- Collaborators: Clinical staff contributing in any way will be mentioned as collaborators

Aim

Critically review and evaluate the processes in the prescribing, administration and monitoring of valganciclovir for cytomegalovirus prophylaxis in liver, kidney or pancreas transplantation.

Objectives

- Define the processes for prescribing, administering and monitoring of valganciclovir use for CMV prophylaxis.
- Identify the procedures available to support decisions in the use of valganciclovir.
- Characterise the harm assessment based on data from prospective audit
- Identify potential and actual risks associated with use of valganciclovir
- Identify pharmaceutical interventions.
- Critically evaluate opportunities for quality improvement by presentation of findings to an expert group.

Methods

- Map the process for prescribing, administation and monitoring of valganciclovir based on interviews with doctors and nurses.
- Collect data regarding adverse drug events associated with valganciclovir from Datix and pharmacist interventions.
- Observe and evaluate process in out-patient setting for prescribing valganciclovir.
- Lastly I will present results and quality improvement suggestions to a multidisciplinary team.