The influence of dental interventions prior to allogeneic haematopoietic stem cell transplantation on patient outcomes and quality of life

Thesis submitted in accordance with requirements of the University of Liverpool for the degree of Doctorate in Dental Sciences: Special Care Dentistry

By

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Abstract

Introduction

National guidance recommends patients receive a dental assessment, and necessary treatment prior to haematopoietic stem cell transplant (HSCT), due to the resulting immunosuppression and increased risk of sepsis. It is uncertain from the current literature what benefits pre-HSCT dental interventions have on patients' outcome post-HSCT. This study aimed to evaluate the effect of dental treatment for allogeneic HSCT recipients on medical outcomes and quality of life.

Methodology

The study was conducted in two parts. The first study was a retrospective review of medical and dental records for 37 patients who received allogeneic HSCT in 2016, and may or may not have received pre-HSCT dental treatment.

The second study was mixed-methods in design exploring seven patients' views of dental services and their post-HSCT medical outcomes using quality of life questionnaires and face-to-face semi-structured interviews.

Results

The first study highlighted positive engagement with dental services from both patients and the medical team, with patients having dental needs prior to transplant. The study revealed more time was available to complete dental treatment prior to transplant. Importantly, although patients

experienced post-HSCT oral complications there was no indication that any diagnosis of sepsis resulted from organisms of odontogenic origin.

From the second study, four key themes emerged: preventing transplant related complications, patient experience of care received, consequences of medical management and psychological impact of treatment. Additionally patients in this cohort expressed a good overall quality of life.

Conclusions

The study was consistent with available evidence, highlighting the need for pre-HSCT dental assessment and review of post-HSCT oral complications. Continuing to provide and improve the current dental service in liaison with medical teams will reassure patients during this vulnerable period. It is still remains unclear what the overall impact provision of dental treatment has on post-HSCT outcomes and therefore, future prospective research is required.

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Glossary

aGvHD	Acute Graft versus Host Disease
AHA	American Heart Association
ALL	Acute lymphoblastic leukaemia
BMI	Body mass index
BPE	Basic periodontal examination
BMTS	Bone marrow transplant subscale
BSDH	British Society of Disability and Oral Health
BSBMT	British Society of Blood and Bone Marrow Transplants
CCC	Clatterbridge Cancer Centre, NHS Foundation Trust
cGvHD	Chronic Graft versus Host Disease
CLL	Chronic lymphoblastic leukaemia
CML	Chronic myeloid leukaemia
DAG	Directed acyclic graph
DMFT	Decayed, missing, filled teeth
EBMT	European Society for Blood and Bone Marrow Transplant
ESH	European School of Haematology
EWB	Emotional wellbeing
FACT-BMT	Functional assessment of cancer therapy – bone marrow transplantation
FWB	Functional wellbeing
GCP	Good Clinical Practice
GDP	General Dental Practitioner
GvHD	Graft versus Host Disease
HLA	Human leukocyte antigen

HODS	Haemato-oncology Diagnostic System
HPHC	High protein high carbohydrate
HPV	Human papilloma virus
HSCT	Haematopoetic stem cell transplant
ICE	Sunquest Integrated Clinical Environment
ID	Identification
IRAS	Integrated Research Application System
ISCT	International Society for Cellular Therapy
IV	Intravenous
JACIE	Joint Accreditation Committee International Society for Cellular Therapy & European Society for Blood and Bone Marrow Transplant
LLLT	Low-level laser therapy
LUDH	Liverpool University Dental Hospital
MDS	Myelodysplastic Syndrome
MRONJ	Medication related osteonecrosis of the jaw
NHS	National Health Service
NG	Nasogastric
NIH	National Institute for Health
NIHR	National Institute for Health Research
NSPT	Non-surgical periodontal therapy
OHI	Oral hygiene instruction
OHIP	Oral Health Impact Profile
OHRQoL	Oral health related quality of life
OMAS	Oral mucositis assessment scale
PBSCT	Peripheral blood stem cell transplant

PENS	Patient Electronic Notes System
POHC	Professional oral health care
PWB	Physical wellbeing
QoL	Quality of Life
RCS (Eng)	Royal College of Surgeons of England
REC	Research Ethics Committee
RIC	Reduced intensity conditioning
RLBUHT	Royal Liverpool and Broadgreen University Hospital Trust
RLUH	Royal Liverpool University Hospital
SCD	Special Care Dentistry
SF-36	Short Form Health Survey
SWB	Social and family wellbeing
TBI	Total body irradiation
TDS	Three times a day
TMJ	Temporomandibular joint
TPN	Total parenteral nutrition
TRT	Transplant related toxicity
VRE	Vancomycin-resistant enterococcus

1 Chapter 1: Introduction

The diagnosis and treatment of a haematological malignancy is a very challenging time for patients, both emotionally and medically, as there are multiple competing demands on their time with numerous hospital appointments to optimize their best opportunity for a successful haematopoietic stem cell transplant (HSCT). Dental assessment and intervention has been recommended in national guidance to improve both intra- and post-transplant outcomes (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). Currently however, there is limited low quality evidence available, as to the extent to which dental treatment improves medical outcomes and quality of life.

1.1 Background

Cancer Research UK reports that there were 9,918 new cases of leukaemia, 5,657 new cases of myeloma, 2,086 new cases of Hodgkin lymphoma and 13,886 new cases of non-Hodgkin lymphoma between 2014-2016 within the United Kingdom (Cancer Research UK, 2016).

Haematopoietic stem cell transplant (HSCT) is used in the treatment of many haematological conditions (British Society of Blood and Bone Marrow Transplantation, 2013, NHS Commisioning Board, 2015). It is also used in the treatment of non-malignant and non-haematological disorders including autoimmune disease (British Society of Blood and Bone Marrow Transplantation, 2013, World Network for Blood and Bone Marrow Transplantation, 2013, NHS Commisioning Board, 2015). Currently over 50,000 HSCTs are carried out annually worldwide, with 50% of these

occurring in Europe (World Network for Blood and Bone Marrow Transplantation, 2013). In 2016, across the British Isles a total of 3,959 stem cell transplants (2,603 autografts and 1,356 allografts) were completed for adult patients (British Society of Blood and Bone Marrow Transplantation, 2016).

1.2 Haematopoietic stem cell transplant

HSCT is the process whereby diseased or malignant blood cells are replaced with healthy stem cells. There are two types of HSCT, allogeneic and autologous, involving different treatment methods and with differing morbidity and mortality rates. The NHS Commissioning Board Document: Clinical Commissioning Policy: Haematopoietic Stem Cell Transplant (NHS Commisioning Board, 2015), defined the types of transplant as:

Allogeneic – "…replacing the bone marrow stems cells of a patient following high dose therapy, with stem cells from a tissue-type matched or mismatched donor…the transplant begins with conditioning therapy… the aim of conditioning is to:

- Kill leukaemia or cancer cells (in malignant disease)
- Eradicate existing bone marrow tissue (in order to provide space for engraftment of transplanted donor cells)
- Suppress the patient's immune system, as to minimise the risk of graft rejection.

... Bone marrow, peripheral blood or umbilical cord blood stem cells may be used as donor stem cell sources." (NHS Commisioning Board, 2015).

Autologous – "…the patient's own stem cells, which are harvested prior to high dose therapy… the therapy destroys the patient's remaining stem cell tissue" (NHS Commisioning Board, 2015).

HSCT is frequently used in the treatment of certain types of leukaemia, lymphoma and multiple myeloma (British Society of Blood and Bone Marrow Transplantation, 2013, World Network for Blood and Bone Marrow Transplantation, 2013).

1.3 Haematopoietic stem cell transplant process

The HSCT process is both complex and specialised with six main stages:

i. **Pre-transplant work up:** involves assessing the suitability and fitness for transplant of both the recipient and the donor, including tissue typing of the donor where applicable (NHS England, 2013).

ii. **Mobilisation/ harvest stage:** collecting the stem cells from; bone marrow, umbilical cord or peripheral circulating blood from either the patient themselves (autologous) or from a matched or mismatched donor (allogeneic) (NHS England, 2013).

iii. **Conditioning:** using cytotoxic drugs, with or without total body irradiation (TBI) (NHS England, 2013, Burke et al., 2014). Dependant on the patient, the regime is either myeloablative (standard regime), or reduced intensity conditioning (RIC) which uses lower doses of cytotoxic drugs and radiation (British Society of Blood and Bone Marrow Transplantation, 2013). The patients are immunosuppressed following conditioning and therefore are admitted to isolation units within the haemato-oncology wards (Burke et al., 2014).

iv. **Infusion:** the harvested stem cells are transferred to the patient via intravenous (IV) infusion. The patient continues to be immunosuppressed and can require blood and platelet transfusions until recovery is confirmed (Burke et al., 2014).

v. **Engraftment:** sign of recovery when sufficient neutrophil numbers are present to reduce infection risk (NHS England, 2013).

vi. **Post-transplant follow-up*:*** dependant on the patient and transplant type along with any witnessed adverse events such as infection or Graft versus Host Disease (GvHD) which may need further input from the multidisciplinary team (NHS England, 2013).

1.4 Complications

1.4.1 Implications for dental assessment

In line with national guidance, it is recommended that patients receive an oral health assessment and appropriate dental treatment prior to undergoing HSCT (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). This aims to exclude any sources of dental pathology that could lead to sepsis during the HSCT process (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

In addition, as a consequence of the conditioning treatment, patients who undergo HSCT become immunosuppressed and thrombocytopenic, placing them at increased susceptibility to infections and bleeding (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

1.4.2 Bisphosphonates

Patients diagnosed with myeloma have additional risks including renal failure and bone disease (National Institute for Health Care and Excellence, 2016). NICE guidelines (National Institute for Health Care and Excellence, 2016) recommend the use of IV bisphosphonates for the treatment of the bone lesions.

The use of IV bisphosphonates impacts on dental management, a potential complication being medication related osteonecrosis of the jaw (MRONJ) (British Society of Disability and Oral Health, 2012, Scottish Dental Clinical Effectiveness Programme, 2017a). It is recommended that, prior to administration of bisphosphonates, dental assessment and appropriate treatment should be provided to reduce the risk of MRONJ for these patients (National Institute for Health Care and Excellence, 2016, Scottish Dental Clinical Effectiveness Programme, 2017b).

1.4.3 Post-transplant oral complications

Oncology patients undergoing chemotherapy, radiotherapy and HSCT are at increased risk of post-treatment complications (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). These complications can include mucositis, xerostomia, candida (fungal) infections and an increased risk of dental caries (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). Therefore targeted pre-operative dental treatment, with particular focus on prevention, is essential to reduce the risk and severity of these complications and to enable patients to manage these complications when they occur (The

Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

Patients undergoing allogeneic HSCT are at risk of the aforementioned complications and, additionally, Graft versus Host Disease (GvHD). GvHD results in a painful mucocutaneous rash as graft cells attack host cells due to a mismatch between the human leukocyte antigen (HLA) of the donor and recipient (Petti et al., 2013, Scully, 2014, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). GvHD is the leading cause of morbidity and mortality in this patient cohort and can be defined as either acute or chronic (Filipovich et al., 2005, Imanguli et al., 2008, Apperley and Masszi, 2012).

Acute GvHD (aGvHD) has previously been defined by its onset, typically within 100 days of transplantation. Currently its diagnosis is based upon clinical and pathological features (Filipovich et al., 2005, Apperley and Masszi, 2012). The lesions of aGvHD usually affect the skin, oral mucosa, gastrointestinal tract, liver or a combination of these organ systems (Filipovich et al., 2005, Imanguli et al., 2008, Apperley and Masszi, 2012).

Chronic GvHD (cGvHD) presents after 100 days post-transplant. However, it should be diagnosed by its presentation as opposed to the time of onset (Filipovich et al., 2005, Apperley and Masszi, 2012). Chronic GvHD can affect any organ system and is the leading cause of death in long-term survivors following HSCT (Imanguli et al., 2008, Apperley and Masszi, 2012).

Therefore, in line with national guidance, there is a need for a dental assessment prior to HSCT to identify and treat any potential causes of infection from the oral cavity (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). This includes providing a preventative regime, restoration of teeth and removal of any teeth of poor prognosis (which could be as a result of acute or chronic infection). It is also important to review these patients with regard to prevention due to the risk of oral complications, mucositis, GvHD and xerostomia, following the transplant period (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

1.5 Care Pathway

There are 55 units across the UK that provide HSCT, of which 10 units solely treat paediatric patients (British Society of Blood and Bone Marrow Transplantation, 2011). The Stem Cell Transplantation and Cellular Therapy Unit, Clatterbridge Cancer Centre (CCC) NHS Foundation Trust, in Liverpool, is one of thirty-seven Haematology units that provides both allogeneic and autologous transplants in the UK (British Society of Blood and Bone Marrow Transplantation, 2011).

Previously the HSCT service was provided by the Royal Liverpool and Broadgreen University Hospitals NHS Trust (RLBUHT). In July 2017 the service was transferred to Clatterbridge Cancer Centre. The service is still operated from the Royal Liverpool University Hospital site, with improvements in diagnostics and the range of services available to patients. At the time of the study the HSCT service was a recognised accredited centre with the Joint Accreditation Committee International Society for

Cellular Therapy and European Society for Blood and Bone Marrow Transplant (JACIE) (JACIE, 2019).

1.5.1 JACIE

JACIE is a mutual committee between the European Society for Blood and Marrow Transplantation (EBMT) and the International Society for Cellular Therapy (ISCT). Accreditation with JACIE ensures that the centre is working within their standards of excellence for patient care and allows for an effective quality management system (FACT-JACIE, 2015). As part of the quality management process auditing is encouraged. EBMT recommended the use and collation of patient data using minimal essential data-AB (MED-AB) forms, allowing patient data to be collected on to a central registry (European Society for Blood and Bone Marrow Transplantation, 2017a). The MED-AB form is separated into:

- ***HSCT MED-A forms*** collect the minimum essential data that is required for EBMT. It collects data at Day 0 (date of transplant), Day 100 and annual follow up. The Day 0 form must be received by EBMT within 10 days of the date of transplant, and the Day 100 form must be received as close to 100 days following transplant or as close to the date of patient death as possible (European Society for Blood and Bone Marrow Transplantation, 2017b).
- ***HSCT MED-B forms*** have two specific forms. There is a disease specific form and a transplant specific form (European Society for Blood and Bone Marrow Transplantation, 2017b).

The Med-A form has been in use since January 2016 in the Stem Cell Transplantation and Cellular Therapy Unit, Clatterbridge Cancer Centre (CCC) NHS Foundation Trust in Liverpool.

1.5.2 Patient journey

There has been an established care pathway between the Stem Cell Transplantation and Cellular Therapy Unit (CCC) and the Special Care Dentistry Department in Liverpool University Dental Hospital since 2013 (Appendix 3). The care pathway was initially developed between Mr A. Kwasnicki, Consultant in Special Care Dentistry, and Dr R. Salim, Consultant Haematologist.

Patients are seen on a referral basis prior to their HSCT and any necessary dental treatment is completed. The dental treatment provided is dependent on the time constraints of the patient's HSCT; some receive comprehensive dental care, others receive essential dental treatment, some require no treatment and others are not referred. Patients are also assessed and treated following emergency referral or post-HSCT. Re-referral post-HSCT allows for review and completion of any non-urgent dental treatment.

Within Liverpool there is currently no data on the impact of dental interventions prior to HSCT on outcomes for this patient cohort, or if the service provided is beneficial from a patient's perspective.

2 Chapter 2: Literature review

A literature review was completed using the databases Ebsco, Medline, PsycInfo and Scopus. The searches were limited from year 2000 to present. Any papers that solely included children, or were unavailable due to limitations in journal access, duplications, or were summaries, or were not available in the English language were excluded from the literature review including book chapters. Further papers were identified from reviewing lists of references within the journals or identified guidance. The literature search was completed on five separate occasions during the study period November 2016 – July 2019, to account for any new publications.

The key terms used within the databases for the searches completed are shown in Appendix 4 and an example search strategy can be found in Appendix 5**.** A summary of the literature acquired from this search can be found in Appendix 6. The SIGN level of evidence (Scottish Intercollegiate Guidelines Network, 1999-2012) used to review the papers is shown in Appendix 7.

The literature review initially focused on the reasons for dental assessment prior to HSCT, the impact of dental treatment on patients receiving HSCT and the effect on the quality of life of dental treatment for patients undergoing HSCT.

2.1 Dental assessment and treatment

It is accepted that a dental assessment and appropriate dental treatment prior to HSCT is necessary to remove dental sources of infection that could impact on post-HSCT recovery and increase the risk of

complications (Epstein et al., 2009, British Society of Disability and Oral Health, 2012, Burke et al., 2014, Elad et al., 2015, Abed et al., 2019).

However, the evidence is limited to show whether dental treatment has a positive impact on patients and actually leads to a reduction in intra- and post-transplant complications.

A retrospective study completed in Israel by Elad et al. (2003) reviewing the time limitations and challenges in providing 'infection-preventing' dental care to patients prior to HSCT (n=46), found that caries was diagnosed in 50% of cases. Of the subjects, 47.8% received oral hygiene instruction (OHI) and scaling, 39.1% had restorations and 19.5% required extractions. The study also discussed the difficulties in organising dental care due to the medical complexities of the patients; although the average time from dental assessment to HSCT was 20.65 days. The authors suggested consideration of the involvement of the Community Dental Service in treating this patient cohort (Elad et al., 2003).

A retrospective study in Japan, by Morimoto et al. in 2004, considered the haematological status of 38 patients prior to dental treatment, as the medical treatments received often resulted in decreased neutrophil and platelet counts. The authors found that it was safe to provide extractions and scaling on patients with platelet counts below $50x10^9$/L or $30x10^9$/L if they had received platelet transfusion. In addition, it was possible to provide extractions and scaling on patients with neutrophil counts between 1.0-$1.5x10^9$/L if antibiotic cover was provided (Morimoto et al., 2004).

The need for dental intervention and haematological consideration for this patient cohort was further supported by a retrospective evaluation completed in the United Kingdom by Durey et al. in 2009. This study reviewed case notes of 94 patients and found that 93.6% of subjects assessed prior to HSCT had active dental disease; 74.5% required interventional dental treatment and 20.2% received OHI. It also highlighted that, although 79.5% of these patients had periodontal disease, screening with a basic periodontal exam was often not performed due to insufficient information about a patient's haematological status given the theoretical risk of bleeding and infection (Durey et al., 2009).

De Paula Eduardo et al., in 2011, carried out a survey of Bone Marrow Transplant Centres in Brazil. The authors of the study found that all responding centres had a dentist as part of their multidisciplinary team. With 100% of the centres (n=36) providing an oral health assessment prior to HSCT. Unfortunately, there was only a 33.3% response rate for this survey with only 12 of the 36 centres responding. It was stated that 75% of the centres advised that they would delay the transplant due to dental pathology whilst 42% felt that oral hygiene was the most important recommendation to provide patients with prior to transplant (de Paula Eduardo et al., 2011).

A retrospective cohort study completed in Brazil, by Pelinsari et al. in 2014 reviewed the extent to which bleeding complications occurred following extractions, for 33 patients prior to HSCT. They found that it was safe to provide extractions in patients who were thrombocytopenic. The authors advised close liaison with the Haem-oncology team and platelet transfusions if the platelet counts were below $50x10^9$/L. This group did not provide

antibiotic cover for this patient cohort unless neutrophil levels were below $0.5x10^9$/L, and found no patient had infective complications. The authors highlighted that this differs from other guidance that recommends antibiotic prophylaxis if neutrophils are less than $2.0x10^9$/L (Pelinsari et al., 2014).

A Brazilian patient survey conducted by Nuernberg et al. (2016) examined patients views (n=110) on accessing dental services prior to HSCT, 66% of those surveyed reported that they had not received guidance about oral care prior to HSCT. However, 74% of subjects reported accessing oral care within a year prior to their HSCT. The study also highlighted issues with oral health care following HSCT with 17% of the subjects being refused treatment by their own dentist and 29% of patients stated they would not trust a dentist to provide treatment outside of the hospital where the transplant took place. Again this study identified the time limitations with regard to providing treatment prior to HSCT (Nuernberg et al., 2016).

Braga-Diniz et al. (2017) reviewed dental records of 188 patients between March 2011 and 2016, to assess their haem-oncology characteristics and their need for endodontic treatment in Brazil. The evaluation found that the need for endodontic treatment pre- and post-HSCT was similar (24.3%:24.7% respectively) and was often indicated for multiple teeth. The paper highlighted the continued need for dental assessment following HSCT, however did not discuss why endodontic treatment was completed as opposed to extractions (Braga-Diniz et al., 2017).

A further Brazilian study by Nuernberg et al. in 2017, assessed the prevalence of periodontal disease within a cohort of 36 patients who were

planned for allogeneic HSCT. They found that the majority of participants (58%) had a diagnosis of periodontal disease with pocket depths >4mm with inflammation. In addition, platelet and neutrophil counts had no influence on bleeding on probing or diagnosis of periodontal disease respectively. The authors highlighted that the patients self-reported that they considered themselves to have good oral health, when in fact the oral health of the cohort was poor. The study emphasised a dental treatment need within this patient cohort, particularly the risk of infection from periodontal pathogens during HSCT and the need for improved periodontal health and oral hygiene. The sample size in the study was small with only 36 participants being included (Nuernberg et al., 2017).

In 2018, a qualitative study was conducted by Mendes et al. in Brazil using face-to-face semi structured interviews to explore patients' views on the meaning of oral health and its importance in HSCT. The authors conducted interviews for 17 participants and used content analysis to finalise three main themes. The themes highlighted by participants were the importance of good oral hygiene, maintaining a good diet, being able to smile and being free from pain. Participants stated the importance of dental assessment pre HSCT was to reduce oral complications, limit the risk of infection and increase the chance of a successful transplant. However the study also highlighted that the referral was requested by medical staff and that treatment with their own dentist was preferable. It appeared the provision of dental treatment was limited for those receiving transplants, as a result of medical barriers such as thrombocytopenia and need for additional medical treatment (Mendes et al., 2018).

Although the literature suggests an overall dental need for these patients to undergo dental assessment, this is limited by the time available to provide necessary treatment prior to HSCT. Unfortunately, although these studies highlighted the dental treatment need within the patient cohort, they did not investigate the effect that dental treatment may have on the HSCT process.

2.2 Dental implications on HSCT outcomes

It is unclear as to what effect dental treatment prior to HSCT has on patient outcomes. A retrospective review completed in the United States of America by Akintoye et al. (2002) compared patients with <20% radiographic crestal bone loss to those with >20% crestal bone loss for levels of septicaemia following HSCT (n=77). Although they found that the patient cohort as a whole was at a higher risk of septicaemia, there was no statistical significance between >20% radiographic crestal bone loss and the incidence of septicaemia (Akintoye et al., 2002).

This was supported by a prospective study completed in Germany by Melkos et al. (2003) which compared two groups of patients undergoing HSCT. In one group, the subjects either did not require or had completed dental treatment (36 subjects) and the other group had no dental treatment (22 subjects) prior to undergoing transplant. Although, those patients who had not received any dental treatment had a higher incidence of post-transplant complications (infection, mucositis, relapse, GvHD) 21/22 subjects compared to 27/36 subjects, the difference was not statistically significant between the groups. Survival rate was also unaffected (Melkos et al., 2003).

A prospective evaluation completed in Japan in 2006, assessed 38 subjects undergoing HSCT, of whom 36 required dental treatment. The aim was to preserve teeth and extract only retained roots, teeth with severe periodontal involvement, symptomatic third molars and teeth with periapical pathology when the time to HSCT was limited. In the study, no subjects encountered odontogenic infection during the period of immunosuppression and, therefore, the authors concluded that radical dental treatment was not necessary. They highlighted a need for early dental screening to allow healing prior to HSCT and additionally, that time pressures had an impact on the clinical decisions made (Yamagata et al., 2006).

A novel way of comparing met and unmet dental needs from the available literature for patients undergoing HSCT was carried out by Elad et al. in 2008, through a decision analysis process. The study showed that by not having a dental evaluation there would be an increased risk of dying from a dental infection of 1.8 in 1000 patients undergoing a HSCT. Although the difference between the groups was small, they concluded that their decision analysis would still recommend that dental assessment and treatment was carried out prior to HSCT (Elad et al., 2008b).

Soga et al. (2008) published a case report, in Japan, of a 53 year old female with AML which highlighted the challenges faced in providing dental treatment. The patient had mild generalised periodontitis with gingival hypertrophy, however, treatment was not provided pre-HSCT due to low platelet and neutrophil counts. Post-HSCT, the patient became septic and died, *Stenotrophomonas Maltophilia* being identified and implicated. The authors highlighted that this patient had no other pre-operative systemic

infection other than periodontitis. They also suggested that the gingivae can act as a reservoir for multi-drug resistant bacteria and recommended periodontal treatment prior to chemotherapy or HSCT to reduce gingival inflammation (Soga et al., 2008).

A prospective study in 2011 conducted by Yamagata et al. in Japan supported the findings that dental intervention had no significant statistical effect on patient outcome post-HSCT (n=35). This study focused on whether leaving asymptomatic impacted third molars in-situ had an effect post-HSCT. The authors found that leaving asymptomatic third molars had no effect on patient outcomes. A statistical difference was found in relation to the duration of post-transplant white cell count being below 1000/µL between those who died (median 17 days) and those who survived (median 13 days) (Yamagata et al., 2011).

A retrospective observational study was completed in Japan to attempt to associate the risk of odontogenic septicaemia with levels of myelosuppression. All subjects (n=37) had a dental assessment and removal of unrestorable teeth. The researchers found that subjects who had moderate and severe levels of myelosuppression were at higher risk of odontogenic sepsis and therefore caution should be taken by the dental team in providing dental interventions. However, the sample size in the study was only 37 subjects and it was therefore concluded that future prospective studies would be required to confirm these findings (Masaya et al., 2013).

In 2014 a further study completed in Turkey, by Ertas et al. compared pre- and post- HSCT DMFT (Decayed, Missing or Filled Teeth) for 36

patients. The authors found that there was an increase in DMFT following HSCT. This study highlighted not only the importance in pre-assessment, but the value of continued dental reviews following HSCT due to the increased incidence of dentally related complications (Ertas et al., 2014).

A retrospective review completed in the United States of America, examined 11 patients with multiple myeloma who had a diagnosis of medication related osteonecrosis of the jaw (MRONJ) found that there was no difference in the incidence of post-HSCT complications (fever, positive blood cultures, length of hospital stay) between MRONJ and non-MRONJ groups. They also found that the staging of MRONJ was not worsened by the HSCT process. However, the sample size in this study was only 11 subjects over a 9 year period, therefore the authors suggested further prospective studies were required (Mawardi et al., 2016).

In 2016, Toro et al. conducted a retrospective review in the United States of America, of patients with myeloma comparing subjects who were dentate (n=90) to those who were edentulous (n=45) and found that no significant differences in post-HSCT complications were found between the groups (Toro et al., 2016).

Although dental assessment and treatment is generally recommended, through local and national guidance prior to HSCT, it is unclear as to the effect that it has on patients' outcomes post-HSCT as there is a paucity of evidence in the literature.

2.3 Post-transplant complications

Following HSCT, complications can occur in the short-term e.g. sepsis, mucositis, or aGvHD, or in the long-term e.g. xerostomia, cGvHD, or secondary malignancies. Both short-term and long-term complications can have an impact on the provision of oral health care (Epstein et al., 2009, British Society of Disability and Oral Health, 2012).

2.3.1 Oral Mucositis

Oral mucositis is a common early post-transplant complication of HSCT, chemotherapy and radiotherapy (Petti et al., 2013, Villa and Sonis, 2015). Over 50% of patients who have had HSCT will experience mucositis (Sonis, 2009, Petti et al., 2013, Villa and Sonis, 2015). Initial presentation is redness (erythema) followed by white plaques and then ulceration of the oral mucosa (Petti et al., 2013).

In HSCT oral mucositis presents within 3-4 days following the infusion and its presentation tends to peak between 7-14 days and then resolves. For patients who have received a combination of chemo-radiotherapy the presentation of mucositis is more severe and prolonged with resolution occurring within 4 weeks (Villa and Sonis, 2015).

Sonis et al., (2001) conducted a prospective observational study in the United States of America, of patients undergoing both autologous and allogeneic HSCT at 8 multinational centres. The severity of mucositis was assessed in 92 patients up to 28 days post-transplant with the use of the Oral Mucositis Assessment Scale (OMAS). It was found that peak mucositis scores were higher among allogeneic transplant patients. Patients having

autologous transplants were at an increased risk of infection associated with their mucositis. Overall it was observed that a higher mucositis score had a 3.9 times increased risk of 100 day mortality (Sonis et al., 2001).

Da Silva Santos et al. (2011) observed the severity and duration of mucositis in 70 patients who had or had not received dental treatment prior to HSCT in Brazil. Although there was no difference in incidence or severity of oral mucositis among subjects, the duration of mucositis in subjects who received a dental assessment +/- treatment was shorter. Those patients who had received dental treatment experienced mucositis for a median of 10 days compared to 20 days in those who did not receive dental treatment (Da Silva Santos et al., 2011).

In comparison, a retrospective analysis conducted in Japan, reviewed all subjects (n = 140) who had a HSCT between February 2002 and December 2009. The authors found that since the implementation of professional oral health care (POHC) in 2006, the incidence of mucositis decreased from 93.5% to 66.7%. (Kashiwazaki et al., 2012).

This was supported by a further observational study in Turkey by Gürgan et al. (2013) which compared periodontal health pre- (n = 202) and post- HSCT (n = 29). Following periodontal treatment they found that, if a subject experienced a reduction in bleeding on probing, the frequency of oral mucositis decreased (Gürgan et al., 2013).

An observational study in Sweden, compared the severity of mucositis in patients who had received either myeloablative conditioning (MAC) (n = 72) or reduced intensity conditioning (RIC) (n = 99) from October 2007 – May

2011. It was found that MAC resulted in significantly higher oral mucositis scores from days 9-12 than RIC and that, since the implementation of their oral health protocol in 2011, the severity of mucositis had decreased. The study also showed a significant correlation between high oral mucositis scores on days 13-24 and prolonged hospital stay (Legert et al., 2014).

A prospective longitudinal study carried out by Barrach et al. in 2015 in Brazil, reviewed the oral complications, caries, periodontal disease, retained roots, oral lesions (mucositis) and infections, for both allogeneic (n = 34) and autologous (n = 31) recipients at 20 days prior to transplant, 7 days post-HSCT and 100 days post-HSCT. No dental interventions were provided, however, they found no increase in caries or periodontal disease and none of the participants experienced infections of odontogenic origin. They found all participants experienced mucositis at day 7 post-transplant, highlighting again, that it is a common oral complication of HSCT (Barrach et al., 2015).

2.3.1.1 Treatment of mucositis

There is evidence of successful treatments for oral mucositis in the period whilst the patient is hospitalised.

The use of Doxepin rinse in an American study showed it to significantly reduce oral pain from mucositis for 9 patients for up to 15 minutes and pain on eating is reduced if used from the initial visit for a week, however the rinse had no effect on the severity of mucositis (Epstein et al., 2008).

Low-level laser therapy (LLLT) has been shown to reduce the severity and duration of mucositis (Khouri et al., 2009, Elad et al., 2011, Patussi et al.,

2014). However, when used in comparison to a placebo, it took until the third visit for a reported reduction in severity and pain to occur. There was no difference between patient satisfaction of the treatments between the groups (study group = 10, control group = 10) (Elad et al., 2011).

2.3.1.2 Patient experiences

A single qualitative study completed in Australia by Borbasi et al. in 2002, explored experiences of mucositis for 6 patients. This study involved weekly in-depth interviews for 4 weeks following HSCT and then at week 8 and week 12 or when resolution of mucositis occurred. The patients within the study felt that with regard to their oral mucositis it was important that the nurses' reminded them about oral health care and the need for mouth care to be considered a therapeutic intervention. They also reported the effect of mucositis on the mouth and oesophagus, the distress caused by eating due to the difficulties in swallowing, and that patients often wondered if the potential curative treatment they had was worthwhile (Borbasi et al., 2002).

2.3.2 Xerostomia

Xerostomia, the experience of a dry mouth, is a further complication of HSCT, and can be an objective or subjective condition. Hyposalivation, a reduced salivary flow rate, is a common experience following HSCT and may be due to disease, medications or the conditioning regime (chemotherapy +/- radiotherapy) (Mauramo et al., 2017).

A cross sectional study completed in the Netherlands by Brand et al., compared the risk of xerostomia in a group of subjects (n =48) having HSCT compared to healthy controls (n = 41). The researchers found that those who

had treatment with HSCT experienced significantly higher levels of xerostomia (Brand et al., 2009).

This finding is supported by a further longitudinal study carried out in Switzerland in 2011, which found that hyposalivation was reported most frequently at 6 months (53%) in patients who had an allogeneic HSCT (n = 228) compared to a control group (n = 141). This symptom continued to 12 months post HSCT with complaints of hyposalivation occurring in 26% of subjects. The study also found that subjects who were conditioned with TBI had higher rates of hyposalivation. The authors concluded that stimulated salivary flow recovered over time, up to 24 months post-HSCT. (Laaksonen et al., 2011).

Bos-den Braber et al., surveyed 96 subjects following HSCT with regards to short- and long-term oral complaints in 2015 in the Netherlands. In 59% of subjects the most frequently reported short-term oral complaint was altered taste. In terms of long-term oral complaints, these were experienced by 28% of subjects with the main complaint being of dry mouth (Bos-den Braber et al., 2015).

A prospective Scandinavian case control study in 2007, found that hyposalivation post-HSCT (n = 118) was most frequent at 6 months and 12 months compared to the control group (n = 247). In contrast to some studies they also found that stimulated salivary flow improved with time. The authors found that subjects were prescribed multiple medications in this time, of which antidepressants was the most common, however this did not

significantly impact on the rate of hyposalivation. They concluded that hyposalivation is multifactorial for this patient cohort (Mauramo et al., 2017).

2.3.3 Graft versus Host Disease

GvHD is a complication for allogeneic HSCT recipients. As previously described, it presents as a painful rash that affects the skin, oral mucosa, gastrointestinal tract and liver and can have an acute or chronic presentation (Filipovich et al., 2005, Lew and Smith, 2007, Imanguli et al., 2008, Apperley and Masszi, 2012, Scully, 2014).

Elad S et al. conducted a prospective longitudinal observational study in Turkey from September 2000 – June 2001 comparing presentation of oral lesions following HSCT, in patients who received autologous HSCT (n = 9) compared to allogeneic HSCT with myeloablative conditioning (MAC) (n = 9) compared to allogeneic HSCT with reduced intensity conditioning (RIC) (n = 16) . They noted no difference in the general presentation of oral lesions or opportunistic infections, however there was a difference in the presentation of oral aGvHD, with this diagnosis being less prevalent in patients who received RIC (Elad et al., 2008a).

A case control study completed in Holland in 2009 observed that 86% of allogeneic HSCT subjects (n = 48) reported GvHD that affected the oral cavity, and found that mucosal pain was more severe (Brand et al., 2009).

Mays et al., (2013) reviewed the literature available on pathogenesis, therapy and research in GvHD and found that 50% of patients who survive 1 year post HSCT will develop oral GvHD and the 5 year mortality rate for those with cGvHD is 70% (Mays et al., 2013).

This is supported by a retrospective study in the United States of America, that examined late effects and complications in patients who have received a second allogeneic HSCT (n =325), and found that GvHD was the overall cause of mortality in 32% of patients over a 10 year period (Duncan et al., 2015).

2.3.3.1 Treatment of GvHD

In an American case report of a patient who was treated for leukaemia with an allogeneic HSCT, who was diagnosed with GvHD 8 months post-transplant after complaining of painful mucosal lesions, it was found that topical corticosteroids were effective in managing the patient's GvHD (Stoopler, 2013).

Yuan et al., carried out a retrospective data analysis in the United States of America, comparing National Institute for Health (NIH) consensus guidance (Filipovich et al., 2005) to current practice in two Oral Medicine departments and three HSCT centres for 79 patients. The authors found that ancillary topical therapies (topical steroids or topical tacrolimus) were prescribed to over half the patients who presented with GvHD. They also found that those treated with topical therapies were five times more likely to have mucositis affecting the oral cavity and three times more likely to have pain involvement from the oral cavity. The study also found that a positive pain score rather than clinical assessment was more likely to prompt treatment in these patients (Yuan et al., 2016).

2.3.4 Secondary Malignancies

Secondary malignancies can be a late complication of allogeneic HSCT, particularly in patients who have been diagnosed with chronic GvHD (Petti et al., 2013, Nappalli and Lingappa, 2015). It has been found that oropharyngeal cancer is the most common secondary malignancy for HSCT recipients, with oral cancer being significantly associated with chronic GvHD (Petti et al., 2013).

This finding is supported by a number of case reports in Brazil, Japan and China, where patients who were diagnosed with chronic GvHD following allogeneic HSCT subsequently presented with oral lesions which were confirmed as oral cancer (squamous cell carcinoma) by histopathology (Torres-Pereira et al., 2014, Tsushima et al., 2015, Weng et al., 2017). An American case report in 2014, presented two cases where the oral cancer was highly reactive for p16/HPV querying the need for HPV (human papilloma virus) screening for this patient cohort (Katz et al., 2014). These case reports highlight the importance of long term surveillance of the oral mucosa for HSCT recipients and continued involvement of the multi-disciplinary team.

2.3.5 Dental intervention

Post-transplant complications of HSCT: mucositis, xerostomia, GvHD and secondary malignancies, support the need not only for pre-operative treatment and prevention advice, but also for long-term dental follow-up (Meier et al., 2011, British Society of Disability and Oral Health, 2012). Patients who have experienced allogeneic HSCT are at risk of experiencing short-term oral pain and difficulties swallowing (dysphagia) due to mucositis

(British Society of Disability and Oral Health, 2012, Bos-den Braber et al., 2015). In addition hyposalivation increases the risk of dental caries for patients and those who develop GVHD are not only at risk of rampant caries but also of long-term secondary malignancies in particular oral cancer (Castellarin et al., 2012, Mays et al., 2013, Petti et al., 2013, Santos-Silva et al., 2015, Mauramo et al., 2017).

2.3.6 Quality of Life

Whilst there were no papers directly examining quality of life of HSCT recipients and their experience of dental treatment, some evidence was available in reference to oral health.

In an observational study in Brazil completed in 2015, 100 subjects were asked to complete an Oral Health Impact Profile questionnaire (OHIP-14) prior to undergoing HSCT. The results were compared to a cohort of healthy volunteers (n = 100) and found that, although weak, there was an impact on oral health related quality of life for potential HSCT recipients especially in the domains of pain and physical disability compared to healthy volunteers. Therefore, the authors recommended pre-operative dental assessment for this patient cohort prior to HSCT (Tinoco-Araujo et al., 2015).

Three further papers were identified at the time of the current study that examined quality of life in this cohort of patients in relation to post-transplant complications.

Silva et al. 2015 completed a randomised control trial in Brazil investigating the quality of life for 39 patients who had treatment of mucositis with low level laser therapy (LLLT) following HSCT. The study used OHIP-14

and Functional Assessment of Cancer Therapy: Bone Marrow Transplant (FACT-BMT) questionnaires to evaluate quality of life. The authors found that there was no difference in quality of life experience reported by the control group (no LLLT) and the study group (treatment with LLLT). However, they found that quality of life was reported to be poorest on day 7 post HSCT with physical and functional wellbeing scoring worst on the FACT-BMT questionnaire (Silva et al., 2015).

This was supported by a Brazilian prospective observational study in 2016, investigating the use of LLLT for treatment of mucositis on quality of life with the use of OHIP-14 and Patient Reported Outcome Measures (PROMS) questionnaires for 69 subjects. They found that quality of life was reported to be poorest 5 days post-autologous and 8-days post-allogeneic transplant and that quality of life subsequently improved with time. Additionally, they found that the domains scoring poorest on the OHIP-14 were psychological disability, social disability and handicap (Bezinelli et al., 2016).

Quality of life in patients with chronic GvHD (n = 569) was investigated in 2015 in the United States of America, using FACT-BMT and SF-36, which assessed overall health status. They found that there was no significant difference in quality of life for subjects who have isolated oral GvHD compared to those with GvHD affecting multiple sites. This study did not look at the impact of chronic GvHD on oral health related quality of life (DePalo et al., 2015).

2.4 Summary

Although there is published evidence in the literature examining the provision of dental treatment and the effect on patient outcomes post-HSCT, the evidence base is limited. From this literature search it was apparent that there were no qualitative studies exploring HSCT and the provision of dental treatment from a patient's perspective. However there has been some work looking at oral health reported outcomes with respect to quality of life.

A gap in the knowledge base exists as to whether a patient understands why dental involvement is important and if they feel the recommendations for and provision of dental treatment had a positive impact on their quality of life. Therefore this research is justified to explore patient views on what affect attending for a pre-HSCT dental assessment had on the HSCT process.

3 Chapter 3: A retrospective evaluation to investigate the incidence of post-HSCT adverse events in patients receiving pre-HSCT dental intervention prior to allogeneic HSCT

3.1 Introduction

The care pathway between the Stem Cell Transplantation and Cellular Therapy Unit (CCC) and the Special Care Dentistry Department has been established since 2013. During this time neither department had investigated the service that was being provided for this particular vulnerable group of patients, therefore the initial part of this project was to evaluate current practice in order to inform service provision and improvement but also to inform future research.

3.2 Title

A retrospective evaluation to investigate the incidence of post-HSCT adverse events in patients receiving pre-HSCT dental intervention prior to allogeneic HSCT.

3.3 Research question

Does dental intervention prior to allogeneic stem cell transplantation influence the incidence of subsequent morbidity and mortality, including graft versus host disease and other oral complications?

3.4 Null Hypothesis

The type of dental treatment received has no influence on patient post-HSCT outcomes.

3.5 Objectives

i. Identify a cohort of patients that received dental intervention prior to allogeneic stem cell transplantation.

ii. Identify and complete patient morbidity and mortality outcome data within the departmental database, using EBMT patient data collection forms.

iii. Investigate the dental intervention factors (including prevention advice and dental treatment) that have been associated with subsequent post-transplant outcomes

iv. Identify if there were any dental interactions on subsequent oral symptoms and complications, including graft versus host disease and sepsis due to oral organisms.

3.6 Methodology

3.6.1 Study design

Ideally a retrospective cohort study would allow comparisons between patients who have received differing levels of dental intervention and those who did not. However, given that the majority of patients are referred to the Dental Hospital for an assessment, an initial retrospective evaluation was required to assess the current patterns and trends for these patients. Therefore, this study was a retrospective study aimed to evaluate patients who had previously received HSCT at Clatterbridge Cancer Centre, Liverpool and who may or may not have received a dental intervention.

The patient cohort was selected and then categorised depending on the dental intervention that they received prior to HSCT from SCD LUDH. The study focused on assessing post-HSCT adverse events to ascertain if there was any difference between those who received dental treatment and those that did not (Appendix 8).

As the study was retrospective, patient data was already available in patient medical and dental records together with electronic patient databases.

3.6.2 Setting

This study included patients under the care of the Stem Cell Transplantation and Cellular Therapy Unit (CCC), Liverpool with the dental care being provided in the Special Care Dentistry Department, RLBUHT, Liverpool.

3.6.3 Population

The study focused on patients who had received an allogeneic HSCT for a haemato-oncological diagnosis (e.g. leukaemia, myeloma, and lymphoma). Allogeneic HSCT recipients were selected as they experience more post-transplant related complications than autologous recipients.

The patients were initially grouped into five cohorts of patients dependant on the different dental intervention that they received prior to allogeneic HSCT.

Those that did not receive dental intervention were considered as the control group. Descriptions of the patients included in each group can be seen in Appendix 8.

3.6.4 Inclusion and Exclusion Criteria

3.6.4.1 Inclusion Criteria

- Adult patients (>18years)
- Allogeneic haematopoietic stem cell transplant
- Patients treated in the Stem Cell Transplantation and Cellular Therapy Unit (CCC)
- HSCT provided from 1st January 2016 – 31st December 2016

3.6.4.2 Exclusion Criteria

- Autologous haematopoietic stem cell transplant
- Patients not receiving allogeneic HSCT at Clatterbridge Cancer Centre, Liverpool
- HSCT provided outside the period of 1st January 2016 – 31st December 2016

- Patients who had a dental intervention but were deceased prior to commencing HSCT
- Patients who were edentulous (missing all their teeth), as referring patients who are edentulous for a dental assessment is currently discouraged.

3.6.5 Outcomes

The study evaluated the incidence of adverse events post-allogeneic HSCT and whether this was influenced by the dental intervention received.

The outcomes of interest in this study were:

i. Experience of sepsis
ii. Experience of mucositis
iii. Experience of xerostomia
iv. Experience of acute GvHD and chronic GvHD
v. Experience of infections (bacterial, viral and fungal)
vi. Experience of mortality at 100 days
vii. Experience of mortality at 1 year

3.6.6 Data Collection Period

In January 2016, the Stem Cell Transplantation and Cellular Therapy Unit (CCC), Liverpool, introduced the use of the EBMT MED-A Day 0 and Day 100 forms. These forms increased the amount and variety of data that was collected for a haematological diagnosis and the HSCT process, therefore the service evaluation took place for 1 year following the introduction of these forms as it was felt that the data would be complete and comparable with other studies within Europe.

The data collection period for this study was the 1st January 2016 – 31st December 2016.

3.6.7 Data Collection forms

An initial data collection form was developed to capture data on social, medical and dental information:

- Patient demographics
- Medical history
- Social history
- Haematological diagnosis, stage, treatment to date (chemotherapy, radiotherapy, bisphosphonates)
- Proposed date of transplant
- Referral for dental intervention; assessment, treatment completed/outstanding
- Transplant process – date, any delay to transplant
- Adverse events – mucositis, xerostomia, neutropenic sepsis, aGvHD, cGvHD, mortality at 100 days and 1 year
- Feeding regime
- Discharge date

This form was sent electronically and reviewed by the HSCT team. The data that was planned for collection was discussed at a meeting on the 27th February 2017 with the Stem Cell Transplantation and Cellular Therapy Unit (CCC) Data Coordinator, Mrs L Laing, and Haemato-oncology Specialist Nurse, Mrs C Hawkins, together with Mrs C Wilson-Dewhurst and Professor S Thompson.

The discussion highlighted the EMBT MED A Day 0 and Day 100 forms and as such the data collection form was adapted to capture additional information and potential confounders to the current and future studies. A final draft of the data collection form can be found in Appendix 9**.**

3.6.8 Data sources

Within Clatterbridge Cancer Centre and LUDH, there were multiple patient databases that were available for review. The different data sources available were also discussed at the meeting on the 27th February 2017, to plan the most accessible way to capture all the data that would be required. The data sources were cross referenced to ensure robust data collection for this study.

The data sources used are listed below with a description of their use:

1. EBMT MED A Day 0 and Day 100 forms: introduced to the Stem Cell Transplantation and Cellular Therapy Unit (CCC) in January 2016 to collect a standardised dataset for each Haematological diagnosis.
2. Haematology (EBMT) data base: along with the MED A forms, this was a separate database to record patient details and diagnoses.
3. Patient electronic notes system (PENS): recording of patient notes in both inpatient and outpatient settings.
4. Unity 2.1: Used by nurses to record clinical notes and observations.
5. Sunquest Integrated Clinical Environment® (ICE): used within the Trust to request special investigations and review blood and histology results.

6. Epro® Digital Dictation: used by the Trust to dictate and view clinical correspondence.
7. Haemato Oncology Diagnostic System (HODS): used by the Stem Cell Transplantation and Cellular Therapy Unit (CCC) to record information on cytogenetics and molecular bone marrow.

The department of SCD was not using electronic patient records at the time of the study. Therefore paper dental patient records were reviewed for those patients identified as having attended for dental assessment and/or dental intervention.

Although radiographs are taken as part of the dental assessment process in the special care dentistry department, data regarding the radiographs taken for this patient cohort did not form part of the data collection for this service evaluation.

3.6.9 Method of data collection

Patients who received an allogeneic stem cell transplant in the year 2016 were identified from the Haematology (EBMT) database. Each case was reviewed against the inclusion criteria and excluded as appropriate. Once identified the cases were assessed as to whether the patient received a dental intervention prior to their allogeneic HSCT, and if so the type of dental intervention they received. Those who had not received a dental intervention were considered as part of the control group (Appendix 8).

The medical records of all of the patients who received allogeneic HSCT were reviewed and data was collected from the various data sources, as per the data collection form. Any absent information was recorded as

missing or unknown. Those who received a dental intervention had their dental records reviewed as part of the data collection process. Patient information was anonymised and each patient was assigned a unique identification number.

The review of patient identifiable records (medical and dental case notes) was completed by CW-D.

3.6.10 Data Analysis

The primary outcome of this study was to compare the incidence of morbidity (mucositis, xerostomia, aGvHD, cGvHD, infections and sepsis) and mortality (at 100 days and 1 year) across the groups identified.

Statistical advice from a Senior Biostatistician in the University of Liverpool, Dr Girvan Burnside, was sought throughout the project. At the initial meeting it was highlighted that the sample to be reviewed, 37 patient records, was too small for any further statistical analysis other than descriptive statistics. Therefore, descriptive statistics such as mean, mode, median along with standard deviation, were used to describe the demographics of the patient cohort and also the experience of each separate adverse event, to provide an overview of the data collected. It was advised that the data should be presented in graphs and tables and for a Kaplan-Meier curve to be used to demonstrate mortality.

Due to the complexities of this treatment and patient cohort there were multiple potential confounders to this study for example:

- Nature of the disease
- Age

- Donor type and quality of match
- Conditioning regime
- Additional medical complexities

Due to the number of confounders it was considered possible to use directed acyclic graphs (DAG) to provide an overview of each adverse event and how the variables could affect both the exposure and the outcomes (Greenland et al., 1999, Suttorp et al., 2015). From the DAG, the variables which would need to be adjusted to allow for statistical analysis to be completed and applied in future projects (Greenland et al., 1999). Confounders found within the study could be presented as directed acyclic graphs (DAGs). These DAGs could then be used in future prospective research studies to allow for statistical adjustment of the confounders.

Data was initially collected, with assigned unique ID, in a password protected Microsoft Office database, it was then transferred to a Microsoft Excel® spreadsheet and then to IBM SPSS® statistical software package for analysis, presenting results in tables.

3.6.11 Ethical approval

The study involved review of medical records for NHS patients therefore sponsorship was agreed with Clatterbridge Cancer Centre (Appendix 2). The dental data was available from a larger service evaluation completed within the Dental Hospital in agreement with the RLBUHT audit team (audit reference AO2845).

Full IRAS application was completed leading to a full ethical review with the Health Research Authority and Health and Care Research Wales (Appendix 1). Ethical approval was gained on the 17th April 2018.

3.6.12 Data management

Patient records were reviewed on hospital password protected computers, each case was provided with a unique identification (ID) and transferred to a password protected database. CW-D was the only person with access to the database.

Following completion of the study all of the data, including raw data, was transferred to the Research and Development team within Clatterbridge Cancer Centre for archiving. The sponsorship team have a contract with Iron Mountain® archiving and so this was arranged by the Research and Development team. Any paper based data with patient identifiable information will be destroyed after one year following completion of the study.

3.7 Results

For the year 2016, 37 patients received an allogeneic HSCT as treatment for a haemato-oncology diagnosis, within the Stem Cell Transplantation and Cellular Therapy Unit (CCC).

3.7.1 Demographics

Of these 37 patients, 19 were male and 18 were female (Table 1), their ages ranged from 24 years to 68 years and the majority (n=13) of patients were in the age category 60-69 years. The mean age of this patient cohort was 52 years (Table 2).

	No. patients	Percentage
Male	19	51.4
Female	18	48.6
Total	37	100.0

Table 1: Gender of patients who received an allogeneic HSCT in 2016

	No. patients	Percentage
18-29	3	8.1
30-39	2	5.4
40-49	8	21.6
50-59	11	29.7
60-69	13	35.1
Total	37	100.0

Table 2: Age of patients who received an allogeneic HSCT in 2016

Most patients lived within the counties of Merseyside and Cheshire, with 2 patients commuting from the Isle of Man for treatment (Figure 1)

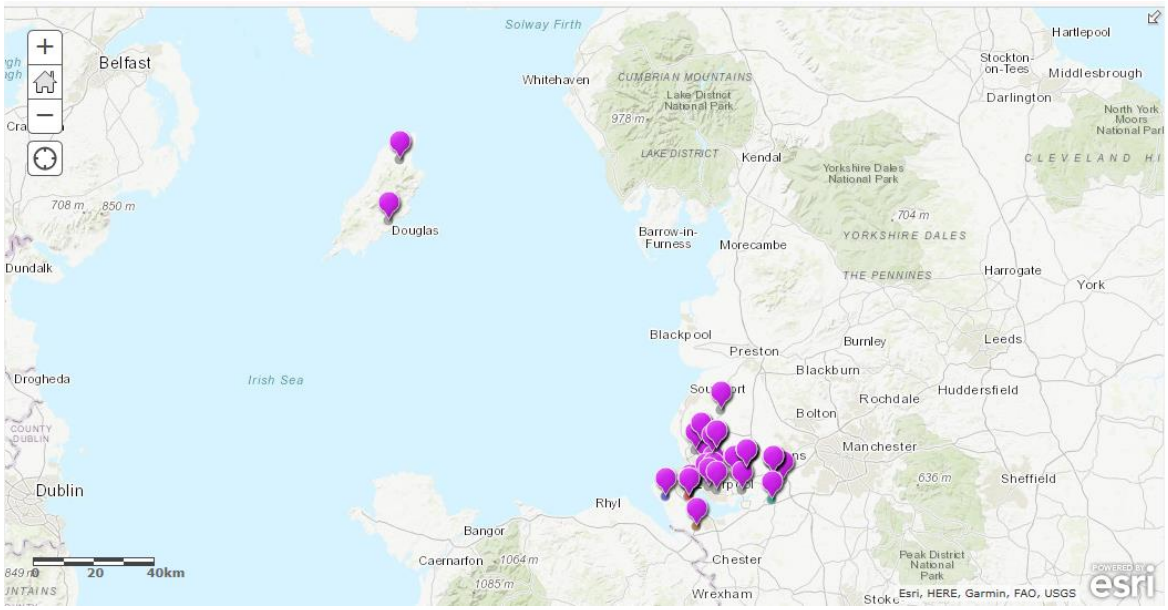
(ArcGIS, 2018). Figure 2 shows the Index of Multiple Deprivation for Merseyside and Cheshire, as be seen on the map the patients in this cohort live in areas that ranged from the most to the least deprived (CDRC maps, 2015).

3.7.2 Medical history

There were 30 patients who reported additional medical comorbidities at the time of dental assessment with 7 patients reporting they had no other medical condition than that of their haemato-oncological diagnosis (Table 3). The additional comorbidities ranged from allergy (n=11), respiratory conditions (n=7), arthritis (n=7) to other diagnosis of cancer (n=3); breast cancer (n=2), renal tumour (n=1). Nine patients reported problems with bleeding, 8 patients were thrombocytopenic, and 1 patient had pancytopenia (Table 4).

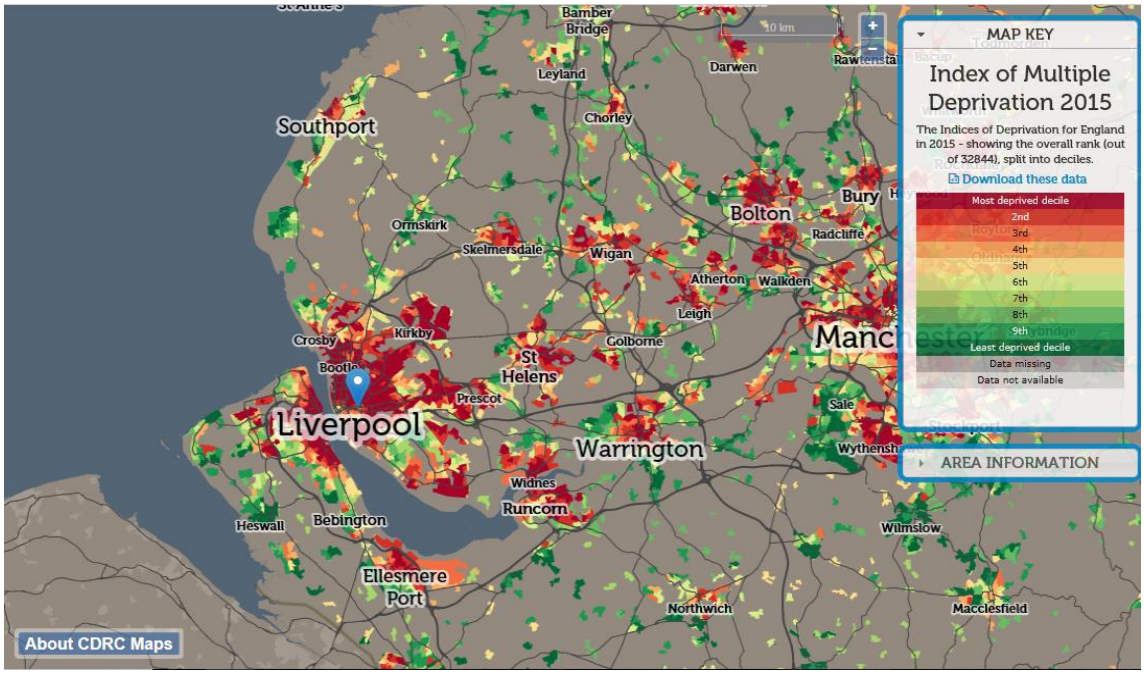
	No. patients	Percentage
Yes	30	81.1
No	7	18.9
Total	37	100.0

Table 3: Any additional medical comorbidities for patients receiving allogeneic HSCT in 2016



https://www.arcgis.com/home/webmap/viewer.html?useExisting=1

Figure 1: Map of geographical distribution of patients within this cohort



https://maps.cdrc.ac.uk/#/geodemographics/imde2015/default/BTTTFTT/10/-2.8462/53.4670/

Figure 2: Map to show Index of Multiple Deprivation for Merseyside

	No. patients (n=30)	Percentage
Allergy	11	36.7
Hayfever	5	16.7
Respiratory conditions	7	23.3
-asthma	*2*	*6.7*
-aspergillous infection	*1*	*3.3*
-shortness of breath	*1*	*3.3*
-history of pseudomonas lung abscess	*1*	*3.3*
-history of pneumonia	*2*	6.7
Cardiac conditions	4	13.3
-myocardial infarction	*1*	*3.3*
-atrial fibrillation	*1*	*3.3*
-hypertension	*2*	*6.7*
Renal conditions	2	6.7
-renal impairment	*2*	*6.7*
Liver conditions	4	13.3
-alcoholic liver disease	*1*	*3.3*
-hepatitis C	*1*	*3.3*
-fatty liver	*1*	*3.3*
-Gilbert's syndrome	*1*	*3.3*
Diabetes	4	13.3
-T1DM	*2*	*6.7*
-T2DM	*1*	*3.3*
-previous	*1*	*3.3*
Cancer	3	10.0
-breast cancer	*2*	*6.7*
-kidney tumour	*1*	*3.3*
Arthritis	6	20.0
-osteoarthritis	*5*	*16.7*
-polymyalgia rheumatic	*1*	*3.3*
Osteoporosis	2	6.7
Mental health problems	2	6.7
-bipolar	*1*	*3.3*
-depression	*1*	*3.3*
Bleeding conditions	11	36.7
-thrombocytopenia	*8*	*26.7*
-pancytopenia	*1*	*3.3*
-subdural haemorrhage	*1*	*3.3*
-subclavian thrombus	*1*	*3.3*
Neurological conditions	3	10.0
-right sided Bell's palsy	*1*	*3.3*
-cerebrovascular accident	*1*	*3.3*
-peripheral neuropathy	*1*	*3.3*
Other	7	23.3
-cholecystectomy	*1*	*3.3*
-eczema	*1*	*3.3*
-fibromyalgia	*1*	*3.3*
-GORD	*1*	*3.3*
-hypothyroidism	*1*	*3.3*
-IBS	*1*	*3.3*
-splenomegaly	*1*	*3.3*

Table 4: Other medical diagnoses for patients receiving allogeneic HSCT in 2016

Five patients were not taking medication other than their chemotherapy agent(s) at the time of their dental assessment. The majority of patients were taking between 1 and 5 medications (n=26) although 1 patient was taking over 10 medications a day (Table 5).

	No. patients	Percentage
0	5	13.5
1-5	26	70.3
6-10	5	13.5
>10	1	2.7

Table 5: The number of medications taken by patients receiving allogeneic HSCT in 2016

Prior to HSCT, 26 patients were diagnosed as being overweight (n=17) or obese (n=9), 11 patients were within the normal weight range (BMI 18.5 to 24.9) (Table 6).

	No. patients	Percentage
Normal weight	11	29.7
Overweight	17	45.9
Obese class I	6	16.2
Obese class II	2	5.4
Obese class III	1	2.7

Table 6: BMI classification for patients prior to allogeneic HSCT in 2016

3.7.3 Social history

At the time of dental assessment, 24 patients reported that they did not smoke with 7 patients reporting that they had smoked previously. Three patients continued to smoke, and the smoking status was unknown for 3 patients (Table 7). The number of cigarettes smoked ranged from 2 per day to 30 per day. In regards to alcohol consumption, 17 patients reported that

they did not drink alcohol, 6 patients rarely drank alcohol and 10 patients reported alcohol consumption (Table 8). The units of alcohol consumed ranged from 1 unit a week to 14 units per week.

	No. patients	Percentage
No	24	64.9
Yes	3	8.1
Previously	7	18.9
Unknown	3	8.1

Table 7: Smoking status at the time of dental assessment for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage
No	17	45.9
Yes	10	27.0
Previously	1	2.7
Rarely	6	16.2
Unknown	3	8.1

Table 8: Alcohol consumption at the time of dental assessment for patients receiving allogeneic HSCT in 2016

3.7.4 Haemato-oncological history

The haemato-oncological diagnosis for this patient cohort can viewed in Table 9. There were 26 patients with a diagnosis of leukaemia, 6 patients had a diagnosis of myeloma and 2 patients had a diagnosis of lymphoma.

There were 7 patients with a predisposing condition; 6 patients had a previous diagnosis of MDS and 1 patient a diagnosis of CML (Table 9). The year of haemato-oncology diagnosis ranged from 1999 to 2016, with most patients (n=14) being diagnosed in 2015 (Table 9).

There were 9 patients who had received a previous autologous HSCT, 3 of these patients had a further autologous HSCT (Table 10). The year of the previous HSCT ranged from 2007 – 2016 (Table 10).

	No. patients	Percentage
Haemato-oncological diagnosis		
ALL	4	10.8
AML	20	54.1
CML	1	2.7
CMML	1	2.7
Follicular lymphoma	1	2.7
IgG Lamda Myeloma	1	2.7
Mantle cell Lymphoma	1	2.7
Multiple Myeloma	5	13.5
Myelodysplastic syndrome	2	5.4
Primary myelofibrosis	1	2.7
Total	37	100.0
Predisposing condition		
No	30	81.1
Yes	7	18.9
• *MDS*	*6*	*85.7*
• *CML*	*1*	*14.3*
Total	37	100
Year of diagnosis		
1999	1	2.7
2007	2	5.4
2009	1	2.7
2011	1	2.7
2012	3	8.1
2013	3	8.1
2014	3	8.1
2015	14	37.8
2016	9	24.3
Total	37	100.0

Table 9: Haemato-oncological background for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage
Number of previous HSCT		
None	28	75.7
1	6	16.2
2	3	8.1
Total	37	100
Year of first HSCT		
2007	1	2.7
2011	1	2.7
2012	1	2.7
2013	2	5.4
2015	3	8.1
2016	1	2.7
Total	9	24.3
Year of second HSCT		
2014	1	2.7
2015	1	2.7
2016	1	2.7
Total	3	3.1

Table 10: History of previous HSCT for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage
Conditioning regime		
Myeloablative	3	8.1
Reduced intensity	34	91.9
Total	37	100
Contraindication to myeloblative therapy		
Patient age	33	89.2
Other comorbidities	1	2.7
N/A	3	8.1
Total	37	100
Type of donor stem cells		
Sibling	10	27.0
Volunteer unrelated donor	27	73.0
Total	37	100

Table 11: Conditioning regime and donor type for patients receiving allogeneic HSCT in 2016

3.7.5 Haematopoietic stem cell transplant

Of the 37 patients, 34 patients received reduced intensity conditioning prior to their HSCT (Table 11). The majority of these 34 patients did not receive myeloablative conditioning due to their age; however, 1 patient had additional comorbidities which prevented the use of myeloablative conditioning (Table 11). In regards to the donor, 27 patients received stem cells from a volunteer unrelated donor, and 10 patients received a sibling transplant (Table 11).

3.7.6 Dental assessment

Within this patient cohort, 36 patients were referred by the Stem Cell Transplantation and Cellular Therapy Unit (CCC) for a dental assessment within the Department of Special Care Dentistry, 34 patients attended their dental assessment (Table 12)

	No. patients	Percentage
Referral to special care dentistry		
Yes	36	97.3
No	1	2.7
Total	37	100
Attended assessment appointment		
Yes	34	91.9
No	3	8.1
Total	37	100

Table 12: Referral and attendance rates to the special care dentistry department for patients receiving allogeneic HSCT in 2016

3.7.6.1 Dental history

There were 23 patients who stated that they had their own general dental practitioners, of whom 22 reported regular attendance (Table 13). For 9 patients their dental attendance was reported as being irregular (>2years),

and dental attendance patterns were not recorded for 3 patients (Table 13) (National Institute for Health Care and Excellence, 2014).

	No. patients	Percentage	Valid percentage
GDP			
Yes	23	62.2	67.6
No	11	29.7	32.4
Total	34	91.9	100
Missing	3	8.1	
Attendance pattern			
Regular	22	59.5	64.7
Irregular	9	24.3	26.5
Unknown	3	8.1	8.8
Total	34	91.9	100
Missing	3	8.1	

Table 13: Patient reported dental attendance for patients receiving allogeneic HSCT in 2016

Regarding oral hygiene regimes, 27 patients reported toothbrushing twice a day, however, toothbrushing was not recorded for 4 patients (Table 14). Only 4 patients reported using interdental cleaning aids (floss and interdental brushes) however, this information was not recorded for 30 patients (Table 14). There were 9 patients who reported the use of mouth wash however, again this information was not recorded for 25 patients (Table 14).

3.7.6.2 Clinical examination

3.7.6.2.1 Extraoral and soft tissue examination

Extraoral examination was completed for all of the 34 patients who attended for dental assessment, for 31 patients nothing abnormal was detected however pallor was noted for one patient and 2 patients experienced clicks to their temporomandibular joints (TMJs) (Table 15). Intraoral examination was documented for all but one patient, 21 patients had

a normal appearance to their soft tissues however abnormalities that were documented include; plaque induced gingivitis (n=1), pallor (n=1), angular chelitis (n=1) and an erythematous lesion on the tip of the tongue (n=1) (Table 16).

	No. patients	Percentage	Valid percentage
Toothbrushing			
Twice daily	27	73.0	79.4
Once daily	2	5.4	5.9
>Twice daily	1	2.7	2.9
Unknown	4	10.8	11.8
Total	34	91.9	100
Missing	3	8.1	
Interdental cleaning			
ID brushes	1	2.7	2.9
Floss	2	5.4	5.9
ID brush and floss	1	2.7	2.9
Unknown	30	81.1	88.2
Total	34	91.9	100
Missing	3	8.1	
Mouthwash			
Yes	9	24.3	26.5
Unknown	25	67.6	73.5
Total	34	91.9	100
Missing	3	8.1	

Table 14: Patient reported oral hygiene regime for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage	Valid Percentage
Nothing abnormal	31	83.8	91.2
Pallor	1	2.7	2.9
TMJ bilateral click	1	2.7	2.9
TMJ left click	1	2.7	2.9
Total	34	91.9	100.0
Missing	3	8.1	

Table 15: Findings from extra-oral examination completed for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage	Valid percentage
Nothing abnormal	29	78.4	85.3
Angular chelitis left	1	2.7	2.9
Pallor consistent with anaemia	1	2.7	2.9
Plaque induced gingivitis	1	2.7	2.9
Erythematous lesion tongue ~5mm	1	2.7	2.9
Not recorded	1	2.7	2.9
Total	34	91.9	100
Missing	3	8.1	

Table 16: Findings from soft tissue examination completed for patients receiving allogeneic HSCT in 2016

3.7.6.3 Dental examination

From the dental clinical examination, 19 patients presented with 58 carious teeth, giving an average number of carious teeth per patient as 1.71 for this patient cohort (Table 17). There were 2 patients who presented with retained roots, 1 retained root per patient (Table 17). There were 5 patients who presented with mobile teeth (Table 17). A total of 31 mobile teeth were documented for these patients; grade 1 mobile teeth (n=11), grade 2 mobile teeth (n=16) and grade 3 mobile teeth (n=4) (Table 17).

3.7.6.4 Periodontal examination

A basic periodontal examination (BPE) was completed for 23 patients, with most patients (n=14) having a highest BPE score of 2 (Table 18). There were 2 patients who scored an asterix (*) indicating either recession, suppuration or furcation involvement (Table 18) (British Society of Periodontology, 2016).

The patients' oral hygiene status at assessment was recorded as good-excellent for 17 patients, satisfactory for 3 patients, and poor/very poor

for 4 patients. Oral hygiene status was not recorded for 10 patients (Table 19).

	No. patients	Percentage	Valid percentage
No. patients with carious teeth	19	51.4	55.9
Total no. carious teeth	58		
Mean no. carious teeth (n=34)	1.71 (+/- 2.08)		
No. patients with retained roots	2	5.4	5.9
Total no. retained roots	2		
Mean no. retained roots (n=34)	0.06		
No. patients with mobile teeth	5	13.5	14.7
Total no. teeth grade 1	11		
Total no. teeth grade 2	16		
Total no. teeth grade 3	4		

Table 17: Findings from dental examination completed for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage	Valid percentage
BPE recorded			
Yes	23	62.2	67.6
Not recorded	11	29.7	32.4
Total	34	91.9	100
Missing	3	8.1	
Total	37	100	
Highest BPE score recorded			
0	3	8.1	13.0
1	1	2.7	4.3
2	14	37.8	60.9
3	5	13.5	21.7
Total	23	62.2	100
Missing	14	37.8	
Total	37	100	
Recession, suppuration or furcation involvement			
Yes	2	5.4	8.7
No	21	56.8	91.3
Total	23	62.2	100
Missing	14	37.8	
Total	37	100	

Table 18: Periodontal assessment for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage	Valid percentage
Excellent	3	8.1	8.8
Very good	1	2.7	2.9
Good	13	35.1	38.2
Satisfactory	3	8.1	8.8
Poor	3	8.1	8.8
Very poor	1	2.7	2.9
Unknown	10	27.0	29.4
Total	34	91.9	100
Missing	3	8.1	
Total	37	100	

Table 19: Operator reported levels of oral hygiene for patients receiving allogeneic HSCT in 2016

3.7.7 Dental treatment

3.7.7.1 Prevention

Oral hygiene advice was documented as being provided for 26 patients, 18 patients received diet advice while 29 received a prescription for high fluoride toothpaste (Table 20). Fluoride varnish was applied for 1 patient (Public Health England, 2017b).

	No. patients	Percentage	Valid percentage
Oral hygiene advice			
Yes	26	70.3	76.5
No	8	21.6	23.5
Total	34	91.9	100
Missing	3	8.1	
Total	37	100	
Diet advice given			
Yes	18	48.6	52.9
No	16	43.2	47.1
Total	34	91.9	100
Missing	3	8.1	
Total	37	100	
High fluoride toothpaste prescribed			
Yes	29	78.4	85.3
No	5	13.5	14.7
Total	34	91.9	100
Missing	3	8.1	
Total	37	100	

Table 20: Documented prevention advice provided to patients receiving allogeneic HSCT in 2016

3.7.7.2 Interventive dental treatment

Table 21 shows the types of treatments received by this patient cohort, 12 patients required no interventive dental treatment (i.e. were dentally stable or were advised that dental treatment could wait until post-HSCT) and solely received preventative advice.

There were 6 patients who completed their dental treatment prior to HSCT, 15 patients had part of their treatment plan completed, or received urgent care such as extractions and temporary restorations. There was 1 patient who refused to have interventive dental treatment, however was given

oral hygiene advice. As stated previously, there were 3 patients who did not attend their dental assessment or were not referred (Table 21).

Type of dental treatment received	**No. patients (n=37)**
All dental treatment has been completed (other than fixed/removable prosthodontics), the patient is deemed dentally stable (Group 1)	6
Only urgent care has been provided (extractions and dressings) or only part of treatment plan has been completed (Group 2)	15
No dental treatment was advised pre-transplant other than prevention advice (Group 3)	12
Refused proposed dental treatment, only received prevention advice (Group 4)	1
No dental treatment received, no prevention advice, patient was not referred or did not attend assessment (Group 5)	3

Table 21: Types of dental treatment provided to patients receiving allogeneic HSCT in 2016

	No. patients	Percentage	Valid percentage
Periodontal treatment provided			
Yes	0	0	0
No	34	91.9	100
Missing	3	8.1	
Total	37	100	
Restorations provided			
Yes	10	27.0	29.4
No	24	64.9	70.6
Total	34	91.9	100
Missing	3	8.1	
Total	37	100	
Total no. restorations completed	20 (range 1-6)		
Extractions provided			
Yes	8	21.6	23.5
No	26	70.3	76.5
Total	34	91.9	100
Missing	3	8.1	
Total	37	100	
Total no. teeth removed	20 (range 1-5)		
Antibiotic prophylaxis prior to extraction			
Yes	7	18.9	87.5
No	1	2.7	12.5
Total	8	21.6	100
Missing	29	78.4	
Total	37	100	
Review to assess healing			
Yes	8	21.6	100
No	0	0	0
Missing	29	78.4	
Total	37	100	

Table 22: Dental treatment provided prior to patients receiving allogeneic HSCT in 2016

3.7.7.2.1 Periodontal treatment

Other than oral hygiene advice no patients in this cohort received interventive periodontal treatment pre-operatively (Table 22).

3.7.7.2.2 Restorative dental treatment

Of the patients who presented with carious teeth (n=19), 10 patients received temporary (n=4) or definitive restorations (n=16) prior to their HSCT (Table 22). A total of 20 restorations were placed for this patient cohort ranging from 1-6 teeth being restored for each patient (Table 22).

3.7.7.2.3 Extractions/surgical dental treatment

Within this patient cohort, 8 patients had extractions (Table 22). A total of 20 teeth were removed ranging from 1-5 teeth being extracted for each patient (Table 22). One patient required enucleation of a cyst which was completed at his extraction appointment.

Of these 8 patients, 7 received antibiotic prophylaxis; 6 patients had pre-operative and post-operative antibiotic cover and 1 patient had solely post-operative antibiotic cover (Table 22).

The most common pre-operative antibiotic regime was 1g Amoxicillin stat dose (n=2) and the most common post-operative antibiotic regime was 500mg Amoxicillin three times daily (tds) for 5 days (n=5) (Table 23 & 24).

	No. patients
500mg amoxicillin, 400mg metronidazole	1
1g amoxicillin, 400mg metronidazole	1
1g amoxicllin	2
2g amoxicillin	1
400mg metronidazole	1

Table 23: Pre-operative antibiotic regime (stat dose) for patients receiving extractions prior to allogeneic HSCT

	No. patients
500mg amoxicillin tds for 5days	5
500mg amoxicillin tds + 400mg metronidazole tds for 5 days	1
400mg metronidazole tds for 5 days	1

Table 24: Post-operative antibiotic regime for patients receiving extractions prior to allogeneic HSCT

	n	No. days	Range
Dental referral and dental assessment	36†	14.9	2 – 63 days*
Dental assessment and dental treatment	16	5.1	1 – 21 days*
Extraction and final review of healing	8	12.1	4 – 36 days*
Discharge from SCD to transplant	34	19.1	6 – 131 days*
Dental referral to transplant	36†	37.4	13 – 143 days*
Dental assessment to transplant	34	23.7	6 – 131 days*
HSCT and neutrophil recovery	37†	11.9	9 – 19 days
HSCT and platelet recovery	37†	13.8	10 – 29 days
Admission date and discharge date	37	31.7	21 – 68 days
Transplant date and discharge date	37	21.9	14 – 43 days
HSCT and aGvHD diagnosis	20	49.0	12 – 85 days
HSCT and cGvHD diagnosis	16	102.8	86 – 136 days
HSCT and relapse	9†	297.9	111 – 563 days
Discharge post-HSCT and relapse	9†	276.4	86 – 520 days
HSCT and death	19	235.7	21 – 652 days
Discharge post-HSCT and death	19	212.2	0 – 624 days
* based on working days: the dental hospital is only open Monday-Friday (9am – 5pm) † incomplete data set			

Table 25: Average number of days between key stages in the transplant process for patients receiving allogeneic HSCT in 2016.

Following extractions, all of the patients (n=8) received a review appointment to assess and confirm healing (Table 22). The average number of days (working days) between extraction and final review of healing was 12.1 days (Table 25).

3.7.7.2.4 Dental treatment outstanding

Items of dental treatment were outstanding in half of the patients (n=17) who attended for dental assessment including those patients who were advised to wait until after transplant to have their dental treatment completed (Table 26). Placement of definitive restorations was delayed most frequently until HSCT was completed (n=10). Additionally, periodontal treatment was planned pre-HSCT for 4 patients however was not completed by either the hygienist or the dentist. Two patients required non-urgent extractions, 2 patients required extra-coronal restorations and 2 patients required addition to or construction of dentures however again it was not possible for this treatment to be completed prior to transplant (Table 27).

	No. patients	Percentage	Valid Percentage
Yes	17	45.9	50.0
No	17	45.9	50.0
Total	34	91.9	100.0
Missing	3	8.1	
Total	37	100.0	

Table 26: Dental treatment that was incomplete at the time of HSCT for patients receiving allogeneic HSCT in 2016

	No. patients
Definitive restoration(s)	10
Extraction(s)	2
Periodontal treatment	4
Advanced restorations	2
Denture construction/adjustment	2

Table 27: Types of dental treatment remaining for patients receiving allogeneic HSCT in 2016

3.7.7.3 Timeline

For this patient cohort, the timeline for completion of dental treatment is shown in Table 25. There was an average of 14.9 working days between the date of referral and the assessment appointment. The time of dental assessment to treatment was 5.1 days, with the time between discharge from SCD and the date of the patient's HSCT being 19.1 days. On average, there was 37.4 days between referral and transplant and 23.7 days between the date of dental assessment and the date of the HSCT.

3.7.8 Post-HSCT outcomes

Following review of the dental records, the medical records were reviewed from the point where the patient was admitted for HSCT. The average length of hospital stay for these patients was 31.7 days with the length of time between transplant and discharge from hospital being 21.9 days (Table 25).

3.7.8.1 Recovery

The recovery of patients' platelet and neutrophil counts were reviewed. There were 36 patients whose neutrophil count recovered (>0.5 x 10^9/L) and 35 patients whose platelet count recovered (>20 x 10^9/L) whilst in hospital (Table 28). The average number of days between HSCT and

neutrophil recovery was 11.9 days and between HSCT and platelet recovery was 13.8 days (Table 25).

	No. patients	Percentage
Incidence of neutrophil recovery		
Yes	36	97.3
No	1	2.7
Total	37	100
Incidence of platelet recovery		
Yes	35	94.6
No	1	2.7
Unknown	1	2.7
Total	37	100

Table 28: Evidence of platelet and neutrophil recovery for patients following allogeneic HSCT in 2016

3.7.8.2 Feeding regime

The feeding regime was variable, with many patients having more than one system for feeding. There were 26 patients who were fed by nasogastric tube and this was often in combination with another food source. There were 20 patients who had a high protein/high carbohydrate diet, 22 patients had additional supplements such as Ensure® build up drinks and 11 patients were described as consuming solid foods (Table 29).

	No. patients
High protein/high carbohydrate diet	20
NG tube	26
Solid foods	11
Supplements	22
Thickened fluids	2
TPN (total parenteral nutrition)	2

Table 29: In patient feeding regimes for patients following allogeneic HSCT in 2016

The BMI for patients on discharge from hospital was calculated from their height and weight on discharge. The weight was not recorded for 13 patients and, therefore a BMI was not calculated. There were 16 patients who were considered overweight or obese and 9 who were of a normal weight (Table 30). Fourteen patients lost weight during the transplant period with the average weight loss being 5.1kg, one patient maintained their weight throughout and 9 patients gained weight with the average weight gain being 4.9kg (Table 30).

	No. patients	Percentage
BMI classification on discharge post-HSCT		
Normal weight	9	24.3
Overweight	12	32.4
Obese I	2	5.4
Obese II	1	2.7
Unknown	13	35.1
Total	37	100
Weight change during transplant		
Weight lossed	14	37.8
Weight gained	9	24.3
Maintained weight	1	2.7
Unknown	13	35.1
Total	37	100
Average weight loss	5.1kg	
Average weight gain	4.9kg	

Table 30: Changes to patients weight following allogeneic HSCT in 2016

	No. patients	Percentage
Experience of mucositis		
Yes	17	45.9
No	20	54.1
Total	37	100
Recorded mucositis score		
None	20	54.1
Mild (1)	8	21.6
Moderate (2)	3	8.1
Severe (3)	1	2.7
Other descriptor	2	5.4
Unknown	3	8.1
Total	37	100
Experience of dry mouth (xerostomia)		
Yes	4	10.8
No/not recorded	33	89.2
Total	37	100

Table 31: Oral complications experienced by patients following allogeneic HSCT in 2016

3.7.9 Post-HSCT complications

3.7.9.1 Oral complications

From an oral complication perspective, there was a record of 17 patients who were diagnosed with mucositis, with the mucositis score mostly being recorded as mild (n=8). One patient experienced severe mucositis (Table 31). There were 4 patients who reported xerostomia (Table 31). Other oral complications that were documented are highlighted in Table 32, with oral candida infections (n=10), oral ulceration (n=7) and a generalised sore mouth/throat (n=7) being recorded more frequently.

3.7.9.2 Infections

Sepsis was documented frequently in this patient cohort, with 25 cases of sepsis being documented during their inpatient stays post HSCT (Table 33). Neutropenic sepsis was only documented clearly in 6 of the

cases with 3 patients diagnosed with septicaemia and 16 cases of unspecified sepsis (Table 32). The infective organism was identified within the notes for 11 patients with sepsis (Table 33). Antibiotics were prescribed for 20 patients (Table 33), with multiple combinations being documented (Table 34). The most frequent was a combination of Tazocin® and teicoplanin.

There were 27 patients where other types of infection were documented, often in combination. The most commonly experienced were viral infections (n=16). Bacterial infections were experienced by 14 patients whilst 13 patients had fungal infections (Table 33).

Complication	Total no.	Examples	No. patients
Oral	45	Mucositis	12
		Sore mouth/throat	7
		Oral/oropharyngeal ulceration	7
		Hyposalivation	4
		Hypersalivation	1
		Oral candida	10
		Dysphagia	1
		Dysguesia	1
		Haemangioma (tongue)	1
		HSV cold sore	1
Sepsis	25	Neutropenic sepsis	6
		Unspecified sepsis	16
		Septicaemia	3
Viral	22	CMV reactivation	13
		Astrovirus reactivation	1
		Adenovirus reactivation	3
		BK viraemia	1
		Coronovirus	2
		HSV cold sore	1
		Shingles	1
Bacterial	7	VRE bacteraemia	4
		CDT infection	1
		C. diff infection	2
Fungal	13	Oral candida	10
		Other candida	2
		Unspecified fungal infection	1
Infection (other)	6	Hospital acquired pneumonia	1
		Perianal abscess	1
		Infected sebaceous cyst	1
		Conjunctivitis	1
		UTI	2
Gastro-intestinal	25	Loose stools/ diarrhoea	15
		Nausea/vomiting	5
		Reflux	2
		Oesophagitis	1
		Subacute intestinal obstruction	1
		Malnutrition	1
Liver	6	Deranged LFTs	5
		Liver failure	1

Complication	Total no.	Examples	No.
Kidney	16	Deranged kidney function / decreased eGFR	7
		Acute kidney injury	9
Heart	5	AF exacerbation/new	3
		Tachycardia	1
Neurological	4	Peripheral neuropathy	1
		Headaches/hallucinations	1
		Pain (muscular)	1
		Electrolyte derangement	1
Bleeding	3	Subconjunctival haemorrhage	1
		Bleeding from mouth	1
		Acute subdural haemorrhage	1
Thrombus	2	Superficial thrombus	1
		Internal jugular vein thrombus	1
Other	21	Engraftment syndrome	5
		aGvHD	7
		Rash	3
		Normocytic anaemia	1
		Oedema	3
		Haematoma	1
		Adverse drug reaction	1

Table 32: Documented complications experienced by this patient receiving allogeneic HSCT in 2016

	No. patients	Percentage
Experience of sepsis		
Yes	25	67.6
No/not recorded	12	32.4
Total	37	100.0
Infective organism identified		
Yes	11	29.7
Unknown	14	37.8
N/A	12	32.4
Total	37	100.0
Experience of other infections		
Yes	27	73.0
No	10	27.0
Total	37	100.0
Type of infection		
Bacterial	2	5.4
Bacterial/ Fungal	2	5.4
Bacterial/ Viral	6	16.2
Bacterial/ Fungal/ Viral	4	10.8
Fungal/ Viral	4	10.8
Fungal	3	8.1
Viral	6	16.2
Not recorded	10	27.0
Total	37	100.0
Evidence of antibiotic treatment		
Yes	20	54.1
Not recorded	17	45,9
Total	37	100.0

Table 33: Infective complications experienced by patients following allogeneic HSCT in 2016

3.7.9.3 GvHD experience

3.7.9.3.1 Acute Graft vs Host disease (aGvHD)

All patients received prophylaxis for aGvHD and each patient was administered ciclosporin, either alone (n=31) or in combination with another drug (n=6) (Table 35).

	No. patients (n=21)	Percentage
Tazocin	2	9.5
Tazocin / teicoplanin	2	9.5
Tazocin / teicoplanin / meropenem	2	9.5
Tazocin / teicoplanin / gentamycin	2	9.5
Tazocin / teicoplanin / pentamidine	1	4.8
Tazocin / teicoplanin / meropenem / gentamycin	1	4.8
Tazocin / clarithromycin	1	4.8
Tazocin / teicoplanin / meropenem / clarithromycin	1	4.8
Teicoplanin	1	4.8
Teicoplanin / meropenem	2	9.5
Teicoplanin / meropenem / gentamycin/ vancomycin	1	4.8
Unspecified IV antibiotics	4	19.0
Not recorded	1	4.8

Table 34: Antibiotic regime used in the treatment of infective complications for patients receiving allogeneic HSCT in 2016

	No. patients	Percentage
ALG (rabbit), ciclosporin	1	2.7
ciclosporin	31	83.8
ciclosporin, Methotrexate	2	5.4
ciclosporin, Mycophenylate	3	8.1
Total	37	100.0

Table 35: Prophylactic medication used for aGvHD for patients receiving allogeneic HSCT in 2016

There were 20 patients in this cohort who experienced aGvHD, with the grade of aGvHD ranging from 1 – 4 (Table 36). The organs affected can be seen in Table 36 and were limited to the skin (n=12), gut (n=12) and liver (n=5). The organ affected most severely was the gut with 4 patients having an aGvHD score of 4 for this organ.

The average number of days between HSCT and a diagnosis of aGvHD was 49.0 days (Table 25).

	No. patients	Percentage
Experience of aGvHD		
Yes	20	54.1
No	17	45.9
Total	37	100.0
Grade aGvHD		
0	17	45.9
1	6	16.2
2	6	16.2
3	4	10.8
4	4	10.8
Total	37	100.0
Organ(s) affected by a GvHD and severity		
No diagnosis of cGvHD	17	45.9
Gut (1)	2	5.4
Gut (2)	1	2.7
Gut (3)	2	5.4
Gut (4), Liver (1)	1	2.7
Gut (4), Liver (2)	1	2.7
Liver (1)	1	2.7
Skin (1)	1	2.7
Skin (1), Gut (1)	1	2.7
Skin (1), Liver (1)	1	2.7
Skin (2)	4	10.8
Skin (3)	1	2.7
Skin (3), Gut (4)	1	2.7
Skin(1), Gut (3)	1	2.7
Skin(2) Gut (1)	1	2.7
Skin(2) Liver (4) Gut (4)	1	2.7
Total	37	100.0

Table 36: Experience of aGvHD for patients receiving allogeneic HSCT in 2016

3.7.9.3.2 Chronic Graft vs Host disease (cGvHD)

Chronic GvHD was diagnosed on average 102.8 days following HSCT (Table 25). There were 16 patients who received a diagnosis of cGvHD

following transplant (Table 37). The extent of cGvHD was often limited (n=12), with 3 patients experiencing extensive cGvHD. The NIH scoring system was not frequently used to described cGvHD with 14 patients not having a calculated score, the other 2 patients were scored as mild (Table 37) (Filipovich et al., 2005, Carpenter et al., 2015).

	No. patients	Percentage
Experience of cGvHD		
Yes	16	43.2
No	20	54.1
No (RIP)	1	2.7
Total	37	100.0
Extent of cGvHD		
Not diagnosed with cGvHD	21	56.8
Extensive	3	8.1
Limited	12	32.4
Not recorded	1	2.7
Total	37	100.0
NIH GvHD score		
Not diagnosed with cGvHD	21	56.8
Mild	2	5.4
Not recorded	14	37.8
Total	37	100.0

Table 37: Experience of cGvHD for patients receiving allogeneic HSCT in 2016

3.7.9.4 Relapse

There were 9 patients who had relapse of their haematological malignancy following HSCT (Table 38). The most common reason for relapse was haematological however graft failure, disease progression and molecular or cytogenetic issues were also causes of disease relapse (Table 38). The average number of days between disease relapse and the HSCT was 297.9 days (Table 25).

	No. patients	Percentage
Relapse of haematological malignancy		
Yes	9	24.3
No	28	75.7
Total	37	100.0
Cause of disease relapse		
No relapse	28	75.7
Graft failure	1	2.7
Haematological	3	8.1
Molecular, Cytogenetic	1	2.7
Progression	2	5.4
Unknown	2	5.4
Total	37	100.0

Table 38: Experience and reason for relapse in patients receiving allogeneic HSCT in 2016

3.7.9.5 Survival status

Survival status is recorded at 100 days post-transplant and 1 year post-transplant (European Society for Blood and Bone Marrow Transplantation, 2017b). At 100 days post-transplant 31 patients were still alive (Table 39). Sixteen patients had died 1 year post transplant (Table 39). There was an average of 235.7 days between date of HSCT and date of death, however this ranged from 21 days to 652 days (Table 25).

	No. patients	Percentage
Survival at 100 days		
Alive	31	83.8
Dead	6	16.2
Total	37	100.0
Survival at 1 year		
Alive	21	56.8
Dead	16	43.2
Total	37	100.0

Table 39: Survival status at 100 days and 1 year for patients receiving allogeneic HSCT in 2016

Figure 3 shows a Kaplan-Meier curve for this cohort of patients, as can be seen from the graph the mortality rate is steady within the first year post-transplant at which point the chances of survival improve.

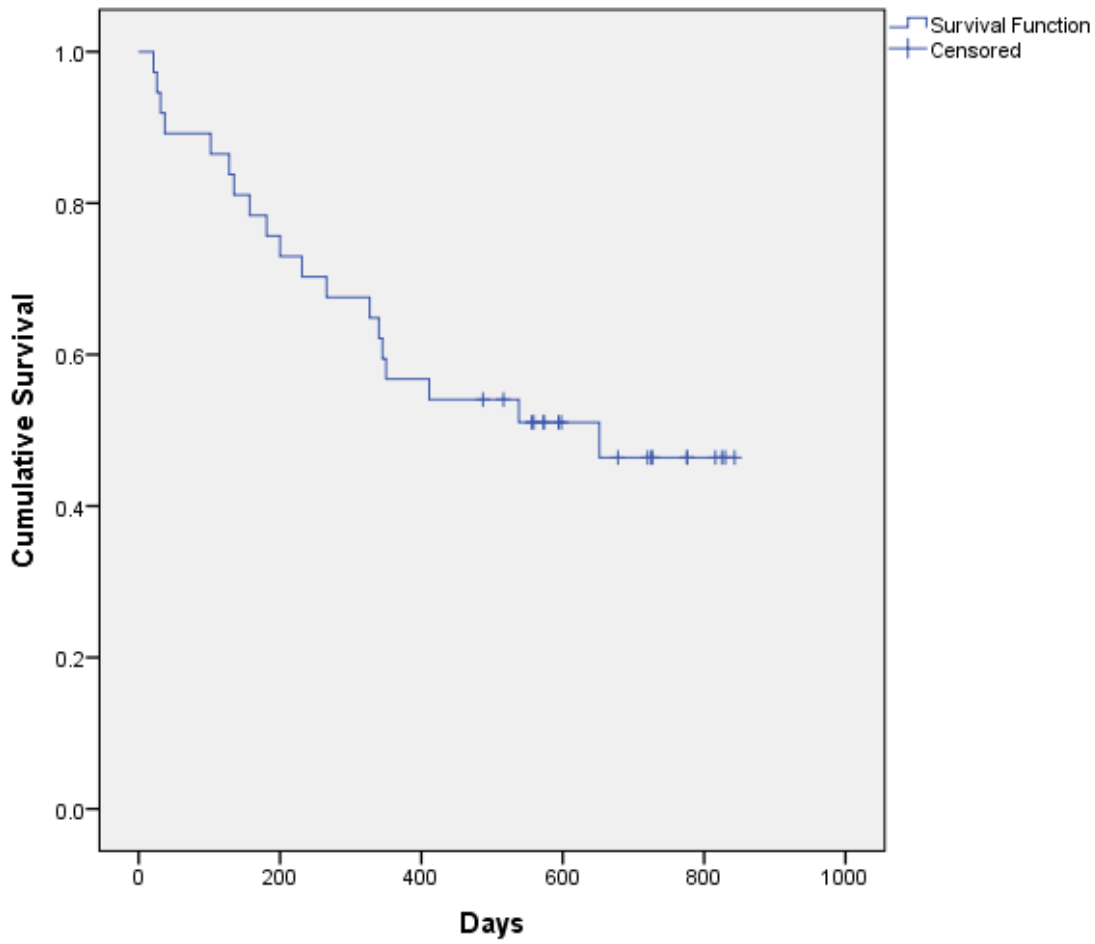


Figure 3: Kaplan-meier curve to show overall survival for patients receiving allogeneic HSCT in 2016

The most prevalent primary cause of death was transplant related (n=10) with relapse or progression of the disease being the main cause of death for 5 patients. The most common secondary cause of death was sepsis (n=9) (Table 40).

	No. patients (n=20)	Percentage
Primary cause		
Relapse/progression	5	25.0
Transplant related	10	50.0
Other	3	15.0
Unknown	2	10.0
Secondary cause		
aGvHD	1	5.0
Cardiac arrest	1	5.0
cGvHD	2	10.0
Frailty	1	5.0
Sepsis	9	45.0
-*E. coli*	1	5.0
-Pneumonia	1	5.0
-Cerebral fungal infection	1	5.0
-Influenza	1	5.0
-Other cause	5	25.0
Stroke	1	5.0
Subdural haematoma	1	5.0
Unknown	2	10.0
No secondary cause	4	20.0

Table 40: Cause of death for patients following allogeneic HSCT in 2016

3.7.9.6 Other complications

Table 32 shows all of the complications documented for this patient cohort. As shown in the table, oral complications were reported frequently, ranging from mucositis to a cold sore. Infections were another commonly documented complication, and patients also experienced gastrointestinal issues, decreased kidney and liver function and complications with bleeding. Three patients experienced an exacerbation or new onset of atrial fibrillation,

4 patients had neurological symptoms whilst other complications included: engraftment syndrome, aGvHD, rashes, allergy and anaemia.

3.7.10 Directed acyclic graph

Completing this study confirmed the complex nature of this patient cohort with multiple confounding factors preventing a confirmation of the causal path between pre-HSCT dental treatment and HSCT outcome. A novel way to represent confounding factors is within a directed acyclic graph (DAG). A DAG was produced, on advice from the Senior Biostatistician (GB) and with the help of a team of Special Care Dentistry clinicians involved in treatment planning and providing dental treatment for this patient cohort (figure 4). Production of this graph provides information for future studies as to the minimal adjustment variables, to allow for a statistical association to be confirmed. For this study, the minimal adjustment variables were:

i. Dental pathology
ii. Haem-oncology diagnosis
iii. Medical comorbidities
iv. Bisphosphonates
v. Obesity
vi. Previous HSCT
vii. Previous chemotherapy
viii. Socio-economic background
ix. Thrombocytopenia
x. Neutropenia

Adjustment of these variables will aid in reducing bias in future studies due to the number of confounding factors and the complex nature of these individuals, their diagnosis and relevant medical treatment.

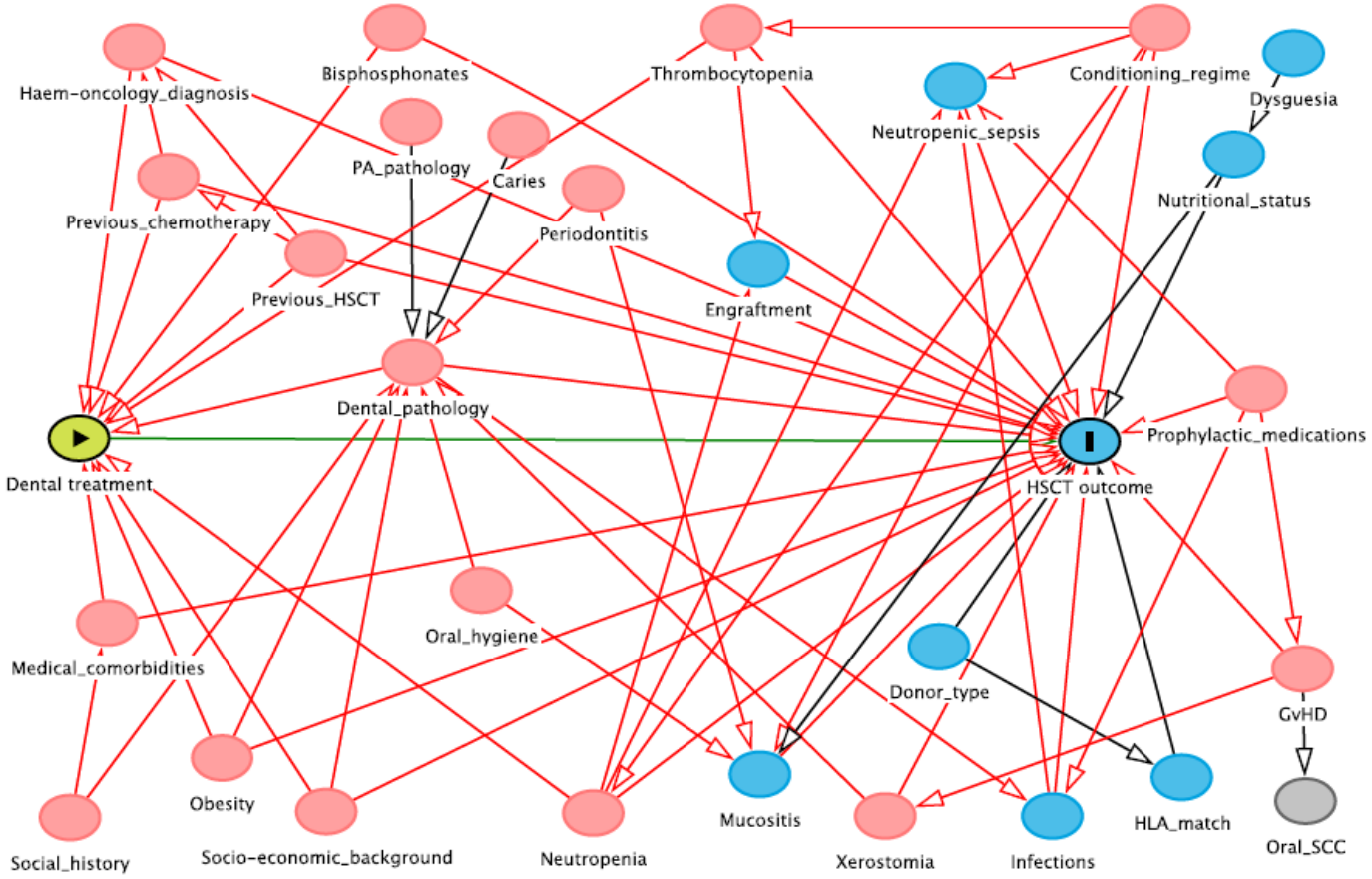


Figure 4: Directed acyclic graph to show potential confounding factors for this patient cohort.

3.8 Discussion

3.8.1 Interpretation of results

In 2016, across the United Kingdom and the Republic of Ireland, there were a total of 1,680 allogeneic haematopoietic stem cell transplants completed, in the treatment of haematological malignancies and non-malignancy related diseases. There were 1,603 primary allogeneic HSCT for adult patients, 324 were primary allogeneic HSCT for paediatric patients and 77 were non-primary allogeneic HSCTs (British Society of Blood and Bone Marrow Transplantation, 2016).

Within the Stem Cell Transplantation and Cellular Therapy Unit (CCC) a total of 37 allogeneic stem cell transplants were completed for patients with a haemato-oncological diagnosis.

3.8.1.1 Demographics

The Stem Cell Transplantation and Cellular Therapy Unit (CCC), provide allogeneic HSCT for adult patients (>18years).

Both the gender and the age of the patients seen within this cohort reflected haematological malignancies affecting any age group or gender (Allart-Vorelli et al., 2015, Bloodwise, 2019). Moreover it highlights the relapsing/remitting nature of the disease, with chemotherapy treatment prolonging life prior to the decision to proceed to a stem cell transplant (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

As a specialist centre for the treatment of haematological diseases the Stem Cell Transplantation and Cellular Therapy Unit (CCC) receives referrals from across the North West region of the United Kingdom. From this particular study the majority of patients were local, within Cheshire and Merseyside (n = 35). Two patients, however, travelled from the Isle of Man for their treatment. Although only a short flight from Liverpool, travelling from the Isle of Man added a further barrier of care for these two patients. An additional referral to the Dental Hospital for a dental assessment and necessary treatment would increase the number of journeys made by these patients. To reduce this barrier attempts were made to ensure appointments were on a day when the patient was already attending the Stem Cell Transplantation and Cellular Therapy Unit (CCC), thus decreasing the impact on care for these patients and their quality of life.

Liverpool and the North West is generally considered as being one of the more deprived areas of the United Kingdom, with a high Index of Deprivation Need (Public Health England, 2017a). More deprived areas tend to experience health inequalities relating to their general and dental health, including higher caries experience (Liverpool Public Health Observatory, 2015).

3.8.1.2 Social history

Within Great Britain 16.6% of the adult population stated they smoked (2018) with 57% of the population (2017) admitting to weekly alcohol consumption of varying amounts. In the current study, the frequency of alcohol consumption and smoking was much lower at 27.0% and 8.1% respectively. This is likely due to the patient's medical team providing specific

health messages at the time of transplant, including smoking cessation advice and advice around reducing alcohol consumption, to improve the overall medical outcome for the patient. Additionally, this was a retrospective study and so it was only possible to collect data that was available hence the lower frequency may be due to under reporting.

Unfortunately within the context of the current study other aspects of social history, including current and previous employment status and family history, were not collected for this cohort of patients.

3.8.1.3 Medical history

Patients within this cohort often had complex medical histories resulting in multiple medications, treatments and numerous hospital appointments.

At the time of dental assessment only 7 patients within this cohort were fit and well, other than their haematological malignancy. The other 30 patients had additional comorbidities of varying severity, ranging from allergy to diagnoses of other cancers. Within the general population comorbidities are common and patients are at risk of developing more than one disease (Department of Health, 2014). The increasing use of reduced intensity conditioning has led to an increased number of HSCTs being provided for older patients and those with additional comorbidities (Alamo et al., 2005).

In the current study, the number and range of medications taken varied considerably amongst patients at the time of the dental assessment and this was reflected in the individual nature of the participants. Some

patients required medication, other than their chemotherapy treatment, to manage other medical comorbidities.

Obesity is an increasing health issue, with over 60% of the adult UK population being defined as obese in 2017 (Cancer Research UK, 2018, NHS Digital, 2019). As with the general population prior to transplant, the majority of patients in this cohort were overweight or obese, with only 11 patients being regarded as a normal weight. In addition, obesity is a risk factor for cancer with 6% of cancers being caused by obesity (Cancer Research UK, 2018).

At the time of the dental assessment appointment, there were 9 patients who stated there were issues with their haematological status. One patient stated that they were pancytopenic (reduced red blood cells, white blood cells and platelets), and the other 8 stated they were thrombocytopenic. Prior to transplant, the expectation would be such that more patients had thrombocytopenia due to their chemotherapy treatment or the disease process (Burke et al., 2014, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018, Abed et al., 2019). This suggests that the majority of patients were unaware at the time of the dental assessment of their potential increased risk of bleeding. Furthermore, it was vital where possible to review the haematological status of these participants at the dental assessment appointment prior to dental treatment. The haematological values for patients who had their haematological investigations at RLUH, could be accessed electronically from the Dental Hospital. The most recent results could be documented and used to plan dental care for the patient, in liaison with the medical team.

3.8.1.4 Haemato-oncological history

The most prevalent haemato-oncological diagnosis was acute myeloid leukaemia (AML) (n = 20). Acute myeloid leukaemia (AML) is the most prevalent type of leukaemia to be diagnosed within the UK (3,100 cases diagnosed in 2015) (Cancer Research UK, 2016). Allogeneic HSCT is the standard of care for patients with a diagnosis of leukaemia, with first line treatment of myeloma and lymphoma being autologous HSCT or being dependant on clinical opinion (British Society of Blood and Bone Marrow Transplantation, 2013).

Predisposing conditions to haematological malignancies such as myelodysplastic syndrome and chronic myeloid leukaemia, both of which can transform to AML, were noted for 7 patients in this cohort.

The year of haematological diagnosis varied over 7 years. Although most patients in this cohort were diagnosed in 2015, there was one patient who received their initial diagnosis in 1999. This particular patient had a diagnosis of myelofibrosis, which was treated with chemotherapy until the allogeneic HSCT in 2016. On the other hand, there were patients within the cohort who were diagnosed and received their transplant in 2016. Other patients had received a previous autologous stem cell transplant in line with the standard of care (British Society of Blood and Bone Marrow Transplantation, 2013). These factors highlighted the complex individuality and varied nature of each case with regards to the diagnosis, prognosis and treatment.

3.8.1.5 HSCT

Prior to the infusion of stem cells, patients who receive an allogeneic stem cell transplant undergo a preparatory conditioning regime. Conditioning involves a combination of chemotherapy treatment with or without radiation (TBI or RIC). The conditioning regime used for allogeneic HSCT is dependent on the donor available, whether they are matched or unmatched, related or unrelated, and the disease itself (European Society for Blood and Bone Marrow Transplantation, 2019a). The ideal conditioning regime for allogeneic HSCT is myeloablative, particularly in cases where the donor is unmatched or unrelated (European Society for Blood and Bone Marrow Transplantation, 2019a). However, myeloablative conditioning regimes have a higher risk of transplant related toxicity (TRT) limiting allogeneic HSCT to patients under 55 years of age who are in good medical health. Reduced intensity conditioning (RIC) regimes have been developed to reduce the TRT and are, therefore, effective conditioning regimes for patients over the age of 55 years or with medical comorbidities (Weisdorf, 2017, European Society for Blood and Bone Marrow Transplantation, 2019a).

Within this cohort of patients, only 3 patients received TBI, the remainder of the cohort received RIC due to their age and medical comorbidities.

According to the European Society of Bone Marrow Transplantation, the ideal allograft donor is a sibling HLA-identical matched donor, yet this is only available in a third of cases worldwide (European Society for Blood and Bone Marrow Transplantation, 2019b). Therefore unmatched sibling donors and matched/unmatched unrelated donors are used. The greater the

disparity in HLA type between recipient and the unmatched donor the poorer the outcome post-HSCT. Within the cohort in this study, the majority of patients received stem cells from volunteer unrelated donors, however the degree of HLA match was unknown as it was not recorded for the purposes of this study (European Society for Blood and Bone Marrow Transplantation, 2019b).

3.8.1.6 Access to dental care

National guidance advises that, prior to chemotherapy, radiotherapy, HSCT and commencement of bisphosphonates, all patients receive a dental assessment and any necessary dental treatment. The aim is to reduce the risk of potential life-threatening infections during the period of immunosuppression and to reduce the potential for medication induced osteonecrosis of the jaw (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

From this study the implementation of the care pathway between the Special Care Dentistry Department and the Stem Cell Transplantation and Cellular Therapy Unit (CCC) was encouraging, with 36 out of the 37 patients being referred for a dental assessment prior to HSCT. There also appeared to be positive engagement from the patients with only 2 patients cancelling or failing to attend their assessment appointments. Unfortunately, at present there is no evidence of referral uptake in the available literature.

The reason for the cancelled appointments was unknown for this patient cohort. From the evidence, this may be due to conflicts with other hospital appointments, medical status or the proximity to their transplant date

(Elad et al., 2003, Yamagata et al., 2006, Durey et al., 2009, Nuernberg et al., 2016).

3.8.1.7 Dental history

As expected the dental history of the patients within the study was varied, with 62% (n=22) of the patients reported having a General Dental Practitioner (GDP), and 22 patients stated that they were a regular attenders. NICE recall guidance was used to assess the attendance status of patients, with regular being classified as seeing a GDP within the last 24 months (National Institute for Health Care and Excellence, 2014). This was a higher rate of reported regular attendance than in other studies. Durey et al. in 2009 conducted a retrospective evaluation and found that a regular attendance pattern was reported to be much lower at 29.8%. However, they found that the patients who saw a dentist regularly required fewer extractions than those who were considered irregular attenders (Durey et al., 2009).

3.8.1.8 Dental examination

National guidance for this patient cohort recommends that all patients should have a full clinical dental examination prior to HSCT, unless there is justification not to, for example, patient refusal or unknown haematological status (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). A clinical examination includes both extra- and intra-oral examination of the soft tissues, periodontal tissue assessment and basic periodontal examination together with notation, charting of the teeth present and relevant radiographic assessment.

Radiographs are taken routinely at assessment for this patient cohort however data regarding radiographic assessment was not collected as part of this service evaluation.

3.8.1.9 Dental pathology

3.8.1.9.1 Periodontal disease

Periodontal disease and the associated periodontal pockets have been highlighted as possible reservoirs for opportunistic infections during and following HSCT (Barrach et al., 2015). Some studies have attributed the cause of infection and sepsis to pathogens involved in periodontal disease (Akintoye et al., 2002, Soga et al., 2008, Masaya et al., 2013).

In addition treatment of periodontal disease, oral hygiene instruction and supra- or sub- gingival scaling can improve gingival inflammation and reduce the severity and duration of mucositis following HSCT (Soga et al., 2008, Gürgan et al., 2013).

Within the current sample, the majority of patients reported twice daily toothbrushing and oral hygiene status was recorded as good-excellent for 17 patients. However, this was a subjective assessment of oral hygiene and so may vary between clinicians. Another study highlighted that although a patient reported good oral hygiene the majority of patients had poor oral health (Nuernberg et al., 2017).

Screening for periodontal disease was completed using a basic periodontal examination (BPE) (British Society of Periodontology, 2019). For patients prior to HSCT the decision to complete a basic periodontal evaluation is dependent on the recent haematological values and state of

immunosuppression for the patient, platelet counts >50x10^9/L and neutrophils counts >1.0x10^9/L. For the cohort, BPE scores were recorded for 68% of patients, with 14 patients having BPE scores of 2 indicating periodontal pockets <3.5mm with plaque retentive factors; overhanging margins or calculus deposits (British Society of Periodontology, 2019). There were 5 patients with BPE scores of 3, indicating periodontal pockets of 3.5mm-5mm and a diagnosis of periodontal disease (British Society of Periodontology, 2019). There were 2 patients who presented with gingival recession.

In addition to BPE, there were 5 patients who presented with mobile teeth ranging from grade 1 (n=11) to grade 3 (n = 4) mobility, again suggesting a diagnosis of periodontal disease. Not all of the patients who presented with tooth mobility had a BPE score completed due to a likely lack of information regarding haematological status.

The number of patients presenting with a diagnosis of periodontal disease within this study was lower than what has been found from the literature where its prevalence ranged from 18.2% - 79.5% (Akintoye et al., 2002, Durey et al., 2009, Nuernberg et al., 2017). However, one of these studies took into account presentation of bone loss on radiographs which was not completed for the current retrospective study (Akintoye et al., 2002). A further study highlighted that calculus deposits were the most common dental finding (Elad et al., 2003). Calculus alone was not documented in the current study as it depended on its recording in the clinical notes. In addition, the evidence also highlights that periodontal disease may be under reported

if it is not possible to complete a BPE screen due to haematological values being unavailable (Durey et al., 2009).

In the current study, no periodontal treatment, including supra-gingival scaling was completed for this cohort of patients, even though treatment was indicated from the BPE scores. Scaling and non-surgical periodontal treatment have been reported within the literature as routine treatments prior to HSCT (Elad et al., 2003, Gürgan et al., 2013, Soga et al., 2008). The lack of periodontal treatment prior to HSCT may be due to unstable haematological values of the patient, time limitations prior to transplant or possible lack of clinical knowledge on the impact that good periodontal health may have on oral complications post-HSCT.

In contrast, 76% of this patient cohort received OHI which has been suggested to be the most important recommendation of a pre-HSCT dental assessment (de Paula Eduardo et al., 2011). However, some studies have reported that patients deny receiving OHI prior to transplant or the advice provided is forgotten even when the patient has received a pre-HSCT dental assessment (Nuernberg et al., 2016, Nuernberg et al., 2017).

3.8.1.9.2 Caries

A further potential reservoir for infection during HSCT is carious teeth. Teeth with cavitated lesions are more difficult to clean and have the potential to harbour opportunistic pathogens such as candida. In addition, larger carious lesions can lead to pulpitis and pulpal necrosis, placing patients at risk of dental pain or periapical infection during HSCT (Barrach et al., 2015).

Teeth with dental caries can be deemed restorable or unrestorable depending on the amount of coronal structure remaining. The treatment options for a tooth are dependent on its restorability, associated symptoms and evidence of periapical pathology or associated infection. All of these factors are taken in to account when treatment planning patients prior to HSCT. The treatment may include simple restorations, endodontic treatment and/or extractions though the treatment plan can be limited by the time available (Bogusławska-Kapała et al., 2017).

In the current study, 56% of the sample presented with caries, with a total of 58 carious teeth. This was higher than in other studies reporting caries experience prior to HSCT, with a number of patients presenting with caries ranging from 7.9% to 52%. However, these studies were conducted in different countries and had varying sample sizes (Elad et al., 2003, Durey et al., 2009, Ertas et al., 2014, Mawardi et al., 2014). In addition to carious teeth, there were two patients within the current sample who presented with retained roots. Evidence of periapical pathology was noted for 4 patients, one of whom presented with a radicular cyst in the upper right quadrant.

3.8.1.9.3 Prevention advice and dental treatment

Prevention advice for these patients is fundamental given the high incidence of dental caries in the cohort. The increased caries risk following the HSCT process results from an increased consumption of carbohydrate based food or drink. Additionally post-transplant complications such as the experience of mucositis, oral GvHD and xerostomia can increase caries risk following transplant. Therefore provision of OHI and diet advice including additional fluoride use is recommended (Public Health England, 2017b, The

Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). However, whilst the haematological values of patients are unstable and the patients are at greater risk for infections and bleeding, the Stem Cell Transplantation and Cellular Therapy Unit (CCC) advise patients against the use of interdental cleaning. Therefore it is important that patients understand the importance of effective toothbrushing throughout transplant, and that OHI is reiterated following HSCT to include the use of interdental cleaning aids.

Within the Department of Special Care Dentistry, the diet advice is tailored to the advice given by the dieticians in the hospital. Weight maintenance and weight gain following transplant has been highlighted as factors that may influence both morbidity and mortality (European Society for Blood and Bone Marrow Transplantation, 2019e). Patients are often encouraged to have a high protein/high carbohydrate diet (HPHC), be fed via nasogastric tube or consume dietary substitutes during the transplant period. HPHC and dietary substitutes have an increase carcinogenicity, however are necessary during this period, therefore dental diet advice is focused on informing patients of the increased caries risk and to rinse with water following build up drinks.

Although the majority of patients in the current study received oral hygiene instruction and the prescription of high strength fluoride toothpaste, within the cohort only 18 patients received documented diet advice, therefore would not be aware of the increased risk of caries.

Ten patients received simple restorations that were either definitive or temporary, with 8 patients having extractions of one or more teeth. The operative treatment provided overall is similar to what has been documented in the literature; with placement of restorations ranging from 21.6 – 45.6% and extraction experience ranging from 19.5% - 40.9% (Elad et al., 2003, Durey et al., 2009, Mawardi et al., 2014). Endodontic treatment is a further option for restoring teeth and it is possible to provide this for transplant recipients (Durey et al., 2009, Braga-Diniz et al., 2017). For this cohort no endodontic treatment was provided, however lack of coronal seal and/or restorability of the tooth or time limitations to transplant may explain why this treatment option was not more readily available.

Antibiotic cover prior to extractions is recommended, in liaison with the oncology team, due to the immunosuppressive nature of the patients within this cohort, although there is currently no strong evidence to suggest any benefit in reducing infection risk. National guidance advises following the American Heart Association (AHA) guidance for infective endocarditis, which suggests a 2g dose of amoxicillin 1 hour pre-operatively (or 2g cephalexin, 600mg clindamycin or 500mg clarithromycin if the is a penicillin allergy), particularly if the patient has neutrophils less than $<2.0x10^9$ (Morimoto et al., 2004, Wilson et al., 2007, Yamagata et al., 2011, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). Other studies have suggested not using antibiotic cover unless neutrophil counts are $<0.5x10^9$ and have not found any additional infective complications (Elad et al., 2003, Pelinsari et al., 2014).

For the cohort in the current study, 7 of the 8 patients received extractions with pre-operative antibiotic cover, however no standardised antibiotic regime was followed. Although amoxicillin was the antibiotic of choice the dose of the drug was usually only 1g. The second line drug, if the patient had an allergy to penicillin, was metronidazole. This varies from the guidance available and highlights the need for a standardised antibiotic protocol within the department, although the evidence to support the benefit of antibiotic prophylaxis for patients is limited (Wilson et al., 2007, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

Patients who had extractions required an additional postoperative appointment to review healing and ensure that epithelialisation had occurred prior to transplant. Therefore, timing of dental treatment needs to be considered thoroughly so that the transplant is not delayed. National UK guidance recommends the review occurs 10 days following extractions. In the current study the average number of days to review healing was 12.1 days, with some patients required more than one review appointment before epithelialisation occurred (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). Unfortunately, this retrospective study did not capture if there were any delays to patients receiving their transplant due to delays with the dental treatment.

3.8.1.9.4 Timing of referral and treatment

Currently there is no consistent guide for the timing of dental referral prior to transplant other than the recommendation that there are at least 10 days for healing following extractions (Durey et al., 2009). Some authors

describe the referral pattern as “hasty” and thus limits the time available for dental treatment, other authors have suggested that referrals made 4-6 weeks prior to transplant would reduce these limitations but that would be dependent on the amount of dental treatment required and availability of appointments (Elad et al., 2003, Yamagata et al., 2006, Durey et al., 2009). For this cohort the dental referral was made on average, 7 weeks prior to transplant however only 6 patients had their full dental treatment plan completed. From reviewing the data, the waiting times for assessment and treatment were prompt being 3 weeks and 1 week respectively. There was an average wait of 4 weeks from discharge from SCD to HSCT during which additional dental care could have been provided. Therefore, closer liaison with the Haem-oncology team is required to assess the time available in order to increase the likelihood of stable oral health.

3.8.1.10 Medical outcomes

There are a number of early and late complications that can affect patients following allogeneic HSCT some of which can impact upon overall survival.

Following the HSCT procedure patients remain in hospital for a period of time, usually up to 6 weeks (Burke et al., 2014). The length of hospital stay was reported to range from 14 – 43 days from the point of transplant to discharge. This is similar to that described in the literature with Toro et al (2016) reporting hospital stays ranging from 3 – 52 days and Mawardi et al (2016) a range of 7 – 22 days.

Patients remain in isolation following HSCT due to their state of immunosuppression, until signs of engraftment are noted. Engraftment is the stage where new bloods cells are formed within the bone marrow including platelets and neutrophils. Both platelet and neutrophil recovery are important factors in the overall survival for these patients. Platelet recovery is defined as platelet count of $>20x10^9$/L for 3 consecutive days, neutrophil recovery is defined as neutrophils $>0.5x10^9$/L over 3 consecutive days (European Society for Blood and Bone Marrow Transplantation, 2017b).

Delayed platelet recovery is likely to occur with higher risk disease and mismatched HLA donors and results in reduced overall survival and increased non-relapse mortality rates (Poon et al., 2013, Akahoshi et al., 2018). Delayed neutrophil recovery can place patients at increased risk of infection and is often managed by the infusion of growth factors, in particular granulocyte colony stimulating factor (Mineishi et al., 2001). A further complication at the time of neutrophil engraftment is engraftment syndrome, a clinical condition where the patient presents with fever, rash, oedema, weight gain and reduced renal and liver function or encephalopathy (Spitzer, 2001, Chang et al., 2014, European Society for Blood and Bone Marrow Transplantation, 2019c). Engraftment syndrome is usually self-limiting, however can lead to multi-organ failure (Spitzer, 2001, Chang et al., 2014, European Society for Blood and Bone Marrow Transplantation, 2016).

Within this patient cohort for all but 2 patients platelet recovery occurred and only one patient failed to experience neutrophil recovery. There were 5 patients who experienced engraftment syndrome and required appropriate medical management.

3.8.1.10.1 Feeding regime and obesity

As previously mentioned, nutritional status of a patient and weight maintenance has a positive impact on a patient's recovery from transplant, risk of infections and overall survival (European Society for Blood and Bone Marrow Transplantation, 2019e). During the transplant process, medical interventions such as chemotherapy, TBI and radiotherapy along with post HSCT short term complications such as mucositis and aGvHD place increased metabolic demands on the patient, with malnutrition being highlighted as a major challenge of HSCT (Espinoza et al., 2016). Oral/enteral feeding regimes are preferable and in the case of gastrointestinal GvHD then parenteral nutrition is necessary (European Society for Blood and Bone Marrow Transplantation, 2019e). Currently, there are no studies to suggest which additional feeding regime dictates better survival rates (Espinoza et al., 2016).

Within the Stem Cell Transplantation and Cellular Therapy Unit (CCC), nutritional support is readily available with patients having a nutritional assessment with the dietician prior to and during transplant. If patients are unable to or struggle with enteral feeding then the use of nasogastric tubes or total parenteral nutrition (TPN) is encouraged. Within the current sample, the feeding regime varied due to the individual nature of each patient. In the 26 patients who had nasogastric feeding, this was often in combination with a further feeding regime. Weight maintenance also varied with some losing whilst other gaining weight.

At the point of discharge from hospital, dieticians could play a role in reiterating diet advice for a patient's future general and dental health. This

would include advice about frequency of eating and consumption of foods with cariogenic potential, to help reduce the caries risk for this patient cohort (Public Health England, 2017b).

3.8.1.11 Oral complications of HSCT

Oral complications can be an early or late consequence of the HSCT process.

3.8.1.11.1 Mucositis

Mucositis is a readily recognised complication of the conditioning process regardless of whether the recipient has had MAC or RIC (Legert et al., 2014, Petti et al., 2013).

Within the existing literature, improvements in oral hygiene and periodontal health have resulted in a reduction in the severity and duration of mucositis (Da Silva Santos et al., 2011, Kashiwazaki et al., 2012, Gürgan et al., 2013). Therefore, this is seen as an important factor in improving pain symptoms and quality of life in the immediate post-HSCT process and further highlights the importance of a pre-HSCT dental assessment to ensure appropriate oral hygiene advice. In addition, continued advice and support with oral hygiene has been shown to be necessary to reduce oral discomfort throughout HSCT (Borbasi et al., 2002).

Furthermore, studies have highlighted different treatment methods in order to improve mucositis symptoms. These include mouthwashes such as doxepin and palmiferin, with the increasing use of LLLT showing positive impacts on patients' quality of life whilst experiencing mucositis (Epstein et

al., 2008, Khouri et al., 2009, Sonis, 2009, Elad et al., 2011, Silva et al., 2015, Bezinelli et al., 2016).

There are a number of scoring systems available to quantify the symptoms and severity of mucositis that would allow consistent recording and more individualised treatment. These include the World Health Organisation Mucositis Scale and the NCI Common Toxicity Criteria both of which combine clinician based observations with a measurement of patient function and ability to eat (World Health Organisation, 1979, National Cancer Institute, 1999, Sonis, 2011). The Oral Mucositis Assessment Scale (OMAS) developed in 1996 aimed for a reliable and valid tool for scoring mucositis for the purposes of research (Sonis et al., 1999, Sonis et al., 2001).

Within the current cohort the recording of mucositis was variable. Mucositis was diagnosed for 17 of the patients, however, there were other records which described a sore or ulcerated mouth with no formal documented diagnosis. There was no consistent mucositis scale in use, with some staff using numerical values and others describing mucositis as mild to severe. In addition, although not recorded within the study, the main treatment for mucositis, within the unit, was the use of diluted chlorhexidine mouthwash and benzydamine hydrochloride to manage symptoms. In addition the unit recommend the use of ice cubes during chemotherapy treatment, to promote vasoconstriction and reduce mucositis symptoms. The use of a consistent mucositis symptom scale would improve patient record keeping and the provision of treatment for mucositis following HSCT.

3.8.1.11.2 Xerostomia

A further common oral complication of HSCT documented within the literature is that of xerostomia (Brand et al., 2009, Laaksonen et al., 2011, Mauramo et al., 2017). Again, a consequence of the conditioning regime prior to transplant, xerostomia can persist for up to 12 months following HSCT and therefore HSCT recipients should be considered as high risk for hyposalivation (Laaksonen et al., 2011, Mauramo et al., 2017). Again the findings suggest that the symptoms of hyposalivation improve with time with fewer recipients complaining of a dry mouth after 12 months post-HSCT (Laaksonen et al., 2011, Mauramo et al., 2017).

Xerostomia is a risk factor for dental caries and therefore for individuals where hyposalivation is a risk factor, targeted prevention advice is of upmost importance. Studies have shown an increase in caries rate following HSCT and thus highlighted the need for continued dental surveillance and prevention advice to reduce the risk of dental caries (Castellarin et al., 2012, Ertas et al., 2014, Public Health England, 2017b, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

Xerostomia was not recorded as a frequent complication of HSCT for this retrospective patient cohort, with it only being documented in 4 cases. This study only collected data of the complications presented during the inpatient period and so whether the patients experienced xerostomia as a long-term complication was unknown. It was also unknown whether the recording of xerostomia was an objective or subjective assessment of the patient.

3.8.1.11.3 Other oral complications

Other oral specific complications for HSCT patients include experience of oral candida infections documented for 10 patients in this sample, and dysguesia, documented for none of the patients within this sample (Brand et al., 2009).

3.8.1.12 Graft versus Host Disease

GvHD presents as a short and long term complication of allogeneic HSCT (Filipovich et al., 2005, Imanguli et al., 2008, Duncan et al., 2015). Acute GvHD presents in the initial phase following allogeneic HSCT whilst chronic GvHD is diagnosed 100 days following transplant, based on the presenting signs and symptoms. GvHD presents as a painful mucocutaneous rash that can affect multiple organ systems, including the gastrointestinal tract, liver and skin (Petti et al., 2013, Scully, 2014, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). Chronic GvHD can affect the overall mortality of patients following HSCT (Mays et al., 2013, Duncan et al., 2015). The presentation of GvHD within the oral cavity, in particular the mucosa and salivary glands results in restricted mouth opening and xerostomia. Therefore there is an increased risk of dental caries for these individuals (Castellarin et al., 2012, Mays et al., 2013).

A severe complication of GvHD is its potential for malignant transformation. Multiple case reports have highlighted the presentation of oral squamous cell carcinoma as a late consequence of allogeneic HSCT (Petti et al., 2013, Katz et al., 2014, Torres-Pereira et al., 2014, Tsushima et al., 2015, Weng et al., 2017).

The consequences of GvHD, mucosal pain, xerostomia, dental caries and its potential malignant transformation, once again highlight the need for continued oral and dental surveillance following allogeneic HSCT either in the primary of secondary dental setting (Castellarin et al., 2012, Katz et al., 2014, Torres-Pereira et al., 2014, Tsushima et al., 2015, Weng et al., 2017, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

There were 20 patients in this sample who experienced acute GvHD with both the site and severity being recorded well. Again for cGvHD the diagnosis was recorded well but the NIH scoring system was not used frequently (Filipovich et al., 2005). This scoring system has been recommended by the EBMT (MED A forms) (European Society for Blood and Bone Marrow Transplantation, 2017b). With both acute and chronic forms of GvHD currently there is no separate score for oral presentation of GvHD and it is likely that this is combined with gut as an organ system.

3.8.1.13 Infections

Infections caused by bacterial, fungal or viral organisms are a severe and life threatening complication of the HSCT process attributed to the neutropenic status of the patient. Neutropenic sepsis is defined as a universal complication of HSCT as a result of the low neutrophil counts and the high levels of bacteria in the bloodstream. In addition, due to the depleted haematological status, fever is often the only sign of infection as the body is unable to form pus, abscess or infiltrates. Therefore, prophylactic antibiotic treatment is paramount for patients during their inpatient stay (European Society for Blood and Bone Marrow Transplantation, 2019d).

As stated previously, dental assessment and treatment is recommended prior to transplant to reduce the risk of odontogenic infections and potential sepsis in the transplant period. However, the evidence to suggest oral causes for sepsis is limited and somewhat contradictory. One study reviewed the micro-organisms that had caused sepsis and that it was possible that their origin was from the oral cavity including the periodontal tissues, however the authors did not find a statistical association between poor oral health and septicaemia (Akintoye et al., 2002). A further study highlighted that dental extraction sites and periodontitis were the preceding causes of sepsis. However, this was only 2 individuals from a cohort of 37 (Masaya et al., 2013). Soga et al. presented a case of a drug resistant bacteria; *S.Maltophilia*, from the gingivae crevice and again highlighted that periodontal tissues were a potential reservoir for infective organisms (Soga et al., 2008).

In contrast, other studies comparing groups of patients receiving pre-HSCT dental treatment with those that had not found none of the patients within the cohorts contracted a systemic infection of odontogenic origin (Melkos et al., 2003, Yamagata et al., 2006, Yamagata et al., 2011).

For the patients within the current study, sepsis was documented for 25 patients, 6 of whom had detailed documentation of neutropenic sepsis. The causal organism was documented, albeit poorly, in only 11 cases, with no odontogenic pathogen being clearly identified as the cause of sepsis. Pathogens identified included pneumococcus, VRE bacteraemia, candida and cytomegalovirus. Antibiotic prophylaxis was documented for 20 of these

patients. Patients were also at risk of other infections, alone or in combination, with viral infections being the most common.

3.8.1.14 Overall survival

Although curative, allogeneic HSCT is associated with multiple life threatening long-term complications, including chronic GvHD, with the majority of deaths occurring within 2 years of transplant (Wingard et al., 2011, Shimoni et al., 2016). Survival following HSCT is dependent on multiple factors out with the scope of this study, including preliminary diagnosis, degree of HLA match, experience of GvHD and relapse (Wingard et al., 2011).

Following the initial 2 year period, 10 year survival rates have been quoted as between 82% - 90% (Wingard et al., 2011). Another study quoted 10 year survival rates for patients with leukaemia as 71% - 73% after the first two years following HSCT, however this decreased significantly if the disease relapsed (Shimoni et al., 2016).

The survival rate for this cohort of patients is represented well within the Kaplan-Meier graph (Figure 3) and highlights the majority of deaths for this cohort occurring within the first 2 years.

Currently the European Society of Bone Marrow Transplantation reviews survival at 100 days post-HSCT and 1 year post-HSCT (European Society for Blood and Bone Marrow Transplantation, 2017b). For this group of patients in this study, 9 patients had experience of disease relapse within (on average) a year of their HSCT. At 100 days post-HSCT, 6 patients had died with a further 10 patients dying within a year post transplant. The most

common primary reason for death was transplant related, however, sepsis was the most common secondary cause of death, again highlighting the high risk of infection for this cohort.

3.8.1.15 Overall outcomes

Unfortunately, the cohort in this retrospective study was too small to compare post-transplant medical complications with dental treatment, as there were only 3 patients who did not attend a dental assessment appointment and therefore did not receive oral hygiene advice or a dental intervention.

Reviewing the data overall, there did not appear to be any difference in complications between those who had good dental health and only required oral hygiene instruction, those who had their dental treatment completed and those who only had part of their treatment plan completed. In a study by Melkos et al. (2003) there was no difference in HSCT outcomes for those patients who received dental intervention to those who did not (Melkos et al., 2003). In addition, another study evaluated post-transplant complications following HSCT in those who were dentate compared to edentulous found no difference in complications between the groups (Toro et al., 2016).

3.8.2 Limitations of the study

There are a number of limitations to this study, the most pertinent being its retrospective nature. Retrospective studies rely upon the relevant information being recorded, documented and available. Within this study, there were examples of suboptimal record keeping, with data missing from

both medical and dental records. In addition, within the medical records, there was no standardised scoring system for mucositis and so this was not recorded clearly. Likewise, although the MED A form requires a NIH GvHD score to be completed this was rarely recorded.

Furthermore, much of what was recorded in patient records was patient reported and relied upon the patient being open and honest for example about their dental attendance and oral hygiene regime. The literature suggests that patients will report better oral hygiene than what is found clinically (Nuernberg et al., 2017). Likewise in the medical records assessment was patient reported and therefore subjective with patients recorded as complaining of a sore mouth or a dry mouth but with no record of a clinical assessment or formal diagnosis.

An additional limitation in regard to record keeping was the change within the Stem Cell Transplantation and Cellular Therapy Unit (CCC) paper records to electronic patient records. Although the paper records were to be available via scanning software, not all of the pages of the paper records had been scanned at the time of data collection and therefore this may account for the missing data. Furthermore, when the use of PENS commenced there was missing electronic data but this decreased with time, as staff were able to better navigate the system. In order to attempt to improve data collection, data was collected from multiple electronic sources and the information compared to try and allow for a more robust data collection. In addition, 20% of the patient records were rechecked for errors to validate the data collection process of which none were observed.

A further limitation of this study was the sample size. On average around 40 allogeneic HSCTs occur within the Stem Cell Transplantation and Cellular Therapy Unit (CCC) each year and in 2016, 37 allogeneic HSCT were completed. The year 2016 was selected as this was the first year the unit was collecting data on the MED A forms. Data collection for 2017 would not have been possible as at the time of data collection (July 2018) not all of these patients within this cohort would have reached 1 year post transplant. Collection of data for subsequent years was not possible within the time constraints of this study.

The limited sample size meant that only descriptive statistics were possible for this sample and therefore no statistical associations were made on advice of the Senior Biostatistician (GB).

Moreover, this study did not evaluate the oral and dental health following transplant. Within the literature there are reports that dental pathology is often noted post-transplant, due to the complications and side effects of medical management, such as xerostomia, mucositis and GvHD. Studies have found increases in DMFT and GvHD associated rampant caries within this patient cohort (Castellarin et al., 2012, Ertas et al., 2014).

A recognised long-term oral complication of HSCT is the malignant transformation of oral GvHD to squamous cell carcinoma, highlighting the increased importance of continued dental surveillance post-HSCT. Current guidance recommends that HSCT recipients are seen within the specialist dental setting for the first 6 months following transplant however, after which if their haematological status is stable, they can be assessed and treated in

the primary dental care setting (Bos-den Braber et al., 2015, Barrach et al., 2015, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

A shared care and multidisciplinary approach to managing this cohort of patients would be ideal in reducing barriers such as access to care (Elad et al., 2003, de Paula Eduardo et al., 2011, Elad et al., 2015). For example, if a patient from the Isle of Man required simple restorations and their haematological status was suitable then they could access treatment closer to home. However, if more complex dental treatment was required or the haematological status was unstable then treatment in a specialist setting would be indicated.

Completion of the study highlighted numerous confounding factors which would need to be considered in future studies to highlight the statistical association between pre-HSCT dental assessment and post-HSCT medical outcomes. For this study the confounding factors have been presented in a directed acyclic graph (see section 3.7.10).

3.8.3 Strengths of the study

Although there were multiple limitations to the study, there are also merits in its completion. The completion of this study has promoted further discussion between the Stem Cell Transplantation and Cellular Therapy Unit (CCC) and the Special Care Dentistry Department. More importantly, knowledge has been gained as to what would benefit future patients, and so service improvements can be developed and implemented, such as production of specific information leaflets on the dental component of the

HSCT patient pathway and the preventative, dietary and oral hygiene advice required throughout the transplant period and beyond.

In addition, the study has reassured the dental team that provision of care is beneficial to patients and was not causing harm. However, from the study it was apparent that there was more time to complete dental treatment prior to HSCT than the treating dental team realised. Therefore, more effective communication is required with patients and their medical team.

Attempts were made to ensure that the data collected was reliable and valid, multiple data sources were used in obtaining a robust data set and ensured minimal information was missed. In addition, 20% of the patient records were rechecked by CW-D to ensure intra-rater reliability and 50% of the dental cases notes were checked by a research supervisor (ST), no additional data was added to the collection during these checks.

An important strength of this study was the creation of a DAG (section 3.7.10), this will aid future research in adjusting for confounders within this cohort of patients to hopefully aid in confirming or rejecting a causal effect between dental treatment and HSCT outcome.

3.8.4 Application to clinical practice

Currently it would be difficult to generalise these results to the whole population of patients receiving allogeneic HSCT given the sample size of 37 patients. Locally, these results will be used in discussions between the Stem Cell Transplantation and Cellular Therapy Unit (CCC). From this research, it has become apparent that closer liaison with Haem-oncology team is necessary to ensure that the time available prior to transplant is utilised

thoroughly with more patients completing the dental treatment required. However, increasing the use of the dental service for these patients would require a review of the service level agreement between the two departments.

There is evidence to suggest that improvements in periodontal and oral health can improve outcomes, namely reducing the severity and duration of mucositis, therefore increasing the focus on prevention and periodontal health, within the time available prior to transplant, may improve patients experience and knowledge around oral complications (Da Silva Santos et al., 2011, Kashiwazaki et al., 2012, Gürgan et al., 2013).

The production of patient information leaflets would be helpful to highlight why a pre-HSCT dental assessment is advised and what treatments a patient might expect prior to and following HSCT. A further information leaflet that covers prevention advice would also be helpful in reminding patients of the positive impact of good oral hygiene experience on their transplant.

Further discussion between the dental and medical teams is necessary to standardise a protocol for antibiotic prophylaxis prior to dental extractions. Currently, there is no standardised protocol used however within the literature and guidance, the AHA guidance for infective endocarditis is cited, prescribing 2g amoxicillin 1 hour prior to treatment with adjustments if there is a penicillin allergy (Wilson et al., 2007, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018). A standard protocol would ensure all patients receive the same standard of

care, although there is limited evidence to suggest that antibiotic prophylaxis prevent infections following extractions.

An additional improvement to the patient pathway would be re-referral following transplant, particularly within the first 6 to 12 months or if the haematological status has not stabilised. This would allow reiteration of diet and oral hygiene advice, monitoring of oral GvHD and oral cancer surveillance. It would also give the opportunity to discuss where future dental treatment could be completed. Again, this would entail a review of the current care pathway and the service level agreement between the two departments.

With this in mind, education of specialist dentists, General Dental Practitioners and the Haem-oncology medical team is important and necessary to establish what treatment is safe to provide and for whom in primary and secondary care environments. This would potentially ease access to dental care for this patient cohort, reducing demands on their time and enable them to be treated closer to home with a dentist who is familiar to them. In addition, further education of the patient's Haem-oncology team in oral health and hygiene would allow them to encourage patients to continue good oral hygiene practices during their HSCT.

From a medical perspective, consistent standardised recording of mucositis and GvHD, using already recognised proformas, throughout the patient journey would ensure correct diagnosis and treatment of these oral complications and should be considered for patients going forward.

3.8.5 Future research

This study has highlighted the difficulties in completing research in this patient cohort due to their complex nature. Possible future studies that could improve the evidence base for these patients would include:

1. An initial survey of primary and secondary dental care providers (community and hospital) to assess whether they have a standardised care pathway for haem-oncology patients and the dental treatment provided.
2. Once centres with a care pathway are identified then a prospective longitudinal multicentre study could be completed over a number of years to investigate the short- and long-term outcomes of dental treatment on HSCT. The DAG developed in this study would be a useful tool in highlighting the variables that require adjustment (Appendix 10).
3. A different research approach could involve quality of life questionnaires and qualitative work to view what patients regard as important during this time and the dental impact prior to HSCT, during HSCT and following HSCT.
4. A further possible future study would be a randomised controlled trial whereby one group of patients receives pre-HSCT dental assessment and treatment and the other does not. However, this would still be limited by the number of confounders and the associated ethical dilemmas as in theory dental treatment prior to transplant reduces the risk of infection for this patient group.

Locally, the results of this study have promoted discussion around this care pathway and improvements have been suggested, therefore in the future possible re-evaluation of the service would continue to assess if a positive impact is being made for patient care.

3.9 Conclusion

Overall, the study highlighted a positive uptake of the care pathway by the Stem Cell Transplantation and Cellular Therapy Unit (CCC) with the majority of patients being referred for a pre-HSCT dental assessment and any necessary treatment. However, issues with communication with the medical team were highlighted and overall, there was more time prior to transplant to allow patients to have their dental treatment completed than understood by the dental team.

Within this cohort, although most patients experienced sepsis in the period directly following HSCT there was no evidence to suggest this was due to an organism of odontogenic lineage. Conversely, the number of patients who experienced sepsis highlights their high risk of contracting an infection due to their immunosuppressive status. Therefore, there remains a need to provide necessary dental treatment prior to transplant, removing possible areas of pathology and reducing risk of sepsis for this cohort, despite the evidence that sepsis is likely to be associated with other pathological sources.

As expected, patients experienced post-HSCT oral complications including mucositis and xerostomia. Providing necessary preventative advice, including diet advice at assessment is necessary to improve their oral health status prior to, during and following transplant to reduce the severity of these conditions and maintain good oral health. Furthermore, patients should receive the necessary advice and information regarding the experience and consequences of oral complications: xerostomia, oral chronic GvHD, dysguesia and stomatitis and additionally the associated increased caries

risk and malignant changes of oral GvHD throughout and following the HSCT process. From a dental perspective these complications highlight the need for continued dental surveillance and preservation of good oral health following transplant.

The study was limited in its retrospective nature, with some elements of the data being poorly recorded or missing. Prospective longitudinal multicentre studies are required to ascertain the actual impact of dental health and provision of pre-HSCT dental assessment for this patient cohort. The use of the directed acyclic graph (Appendix 10) within these studies would be useful in adjusting for the number of confounding factors that are present for this complex cohort of patients.

Although this study is not able to quantify the impact of dental assessment and treatment pre-HSCT for this patient cohort, it does highlight that these patients do present with dental pathology and experience post-HSCT oral complications. Therefore, continuing to provide dental care for these individuals is necessary to reduce the infective risk and attempt to improve oral symptoms directly following transplant. Improved liaison with the patients' multi-disciplinary team is necessary to ensure opportunity to complete dental treatment pre-transplant is maximised, taking into account medical status, need for transplant but also their own decisions when presented with the dental treatment plan and the risks and benefits of and patient choices regarding dental care.

Further studies for this patient cohort are required to quantify the impact of dental treatment on a patient's medical outcome and quality of life.

4 Chapter 4: Describe and explore a patient's outlook on dental care in the context of their medical diagnosis and treatment prior to and following allogeneic HSCT

4.1 Introduction

Chapter 3 evaluated the dental service that is currently being provided for patients prior to allogeneic HSCT and the oral and medical complications that this cohort of patients face following the treatment.

Chapter 4 aims to gain a patient's perspective on both dental treatment and medical complications through semi-structured interviews and quality of life questionnaires at a point of medical stability following allogeneic HSCT.

The study had a mixed methods approach with qualitative methods being selected to enable an in-depth understanding of the topic area and explore human experiences and behaviour (Braun and Clarke, 2006), and quality of life questionnaires providing a quantitative snapshot of the patients view of their current state and quality of life.

4.2 Title

Describe and explore a patient's outlook on dental care in the context of their medical diagnosis and treatment prior to and following allogeneic HSCT.

4.3 Objectives

Explore the views of patients that had received an allogeneic stem cell transplant and a special care dental assessment, focusing on:

1. The dental care pathway.
2. Oral and dental complications.
3. Quality of life after allogeneic stem cell transplant.

4.4 Methodology

4.4.1 Study design

The second part of the research project explored patients' views of their experiences of the care pathway between the Stem Cell Transplantation and Cellular Therapy Unit, Clatterbridge Cancer Centre (CCC), Liverpool and the Special Care Dentistry Department, Liverpool University Dental Hospital, and the physical and emotional complications experienced during and following the HSCT process.

This study involved a mixed methods design, with participants completing validated quality of life questionnaires prior to a face-to-face semi-structured interview.

The quantitative quality of life questionnaires used in this study were:

1. Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (FACT-BMT) (Appendix 11). This questionnaire assesses patients' views on their physical well-being, social/family wellbeing, emotional wellbeing, functional wellbeing and if there are any additional concerns (McQuellon et al., 1997, FACTIT, 2010, Bassim et al., 2014).
2. Lee Chronic Graft vs Host Disease Symptom Scale (Appendix 12). This self-reported questionnaire requests patients state if they have experienced any problems in the last month with their skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy and any mental or emotional problems (Lee et al., 2002, Merkel et al., 2016).

3. Oral Health Impact Profile-14 (OHIP-14) (Appendix 13). This questionnaire evaluates functional limitations, physical pain, psychological discomfort, physical disability, psychological disability and social disability in relation to a patient's teeth, mouth or dentures (Slade, 1997, Slade, 1998).

These questionnaires allowed for a comprehensive evaluation of a patient's quality of life with regards to their experience of the allogeneic bone marrow transplant, their experience of cGvHD, and their oral health.

For both FACT-BMT and Lee cGvHD symptom score permission was sought from their publishers. Email correspondence and agreement for its use was received from Dr Lee and the study was registered online with FACT-IT by the principal investigator (AP).

4.4.2 Population and sampling

For this study patients were sampled from a Late Effects Clinic within the Stem Cell Transplantation and Cellular Therapy Unit (CCC), Liverpool. Patients were considered for inclusion if they were medically stable, had received an allogeneic stem cell transplant and had been assessed and/or had received treatment in the Special Care Dentistry Department.

Ideally for qualitative research a purposive sample is used in that the research team decides who to include within the study, aiming to recruit a variety of participants with different backgrounds, providing a range of views and experiences (Ritchie et al., 2014b). A sample framework was developed (Appendix 14) to allow monitoring of patient selection and aim to reduce bias.

However, due to the low number of patients receiving allogeneic HSCT, a convenience sample was used, thus recruiting patients who were available to be interviewed and met the recruitment criteria.

4.4.3 Setting

An office space in the Stem Cell Transplantation and Cellular Therapy Unit (CCC) was used as the setting for this part of the study. This allowed the interviews to be completed following the participants review appointment on the Late Effects Clinic, and in an environment that was familiar to them. Additionally, it ensured the availability of medical staff should participants express any additional worries or concerns related to their medical diagnosis or treatment.

Different settings were considered for the interviews prior to agreeing on an office space within the Stem Cell Transplantation and Cellular Therapy Unit (CCC) including:

1. Participants own home
2. Office space within the dental hospital

Both of these settings had their merits however these were outweighed by the lack of specialist support from the Haemato-oncology team and the possible effect of a dental setting on patients who were dentally anxious or phobic.

4.4.4 Recruitment

The timing of recruitment of participants was considered, in order to enable the patient to be medically stable, it was decided to recruit patients

from the Late Effects Clinics, in the Stem Cell Transplantation and Cellular Therapy Unit (CCC), when they are over 100 days post-transplant.

Recruitment was completed by CW-D who attended the Late Effects Clinic to recruit participants and complete the interviews.

Other possible times of recruitment that were considered included:

1. Time of the dental assessment in the Special Care Dentistry Department
2. On discharge from the Special Care Dentistry Department following assessment and/or treatment
3. On discharge from the Haemato-oncology ward following HSCT.

These options were discounted as they are at a time when potential participants have increasing amounts of information to consider and retain in relation to their diagnosis, the HSCT process, the risks and benefits of treatment and the need for other medical interventions. In addition, recruitment at the dental assessment would increase the period of time to the interview and the medical outcome for the patient would be unknown.

A particular challenge encountered in recruiting participants was the flexible nature of the late effects clinic. Although patients had an appointment time they were often required to have bloods or see the nurses on the day ward prior to attending the outpatient department. In addition after their appointment they may have other appointments, further blood tests or other infusions. Therefore, initially it was difficult to arrange a date and time for the interview to take place. Following a number of failed attempts, it was decided to ask the participant to choose the date and time of the interview. This was

usually following their clinic appointment when they had a better idea of the demands of their day and the time they would be available for the interview.

4.4.4.1 Participant selection

Participant selection was dependent on the following criteria:

- Allogeneic HSCT only
- Haematological – oncological diagnosis; CLL, CML, ALL, lymphoma, myeloma, failed autograft
- Dental assessment and/or treatment at Liverpool University Dental Hospital
- Dental intervention not completed by CW-D
- Capacity to consent
- Ability to speak fluent English

Appendix 15 shows a flow chart that was used to assess eligibility for inclusion. Recruitment took place on the Late Effects Clinic from 1st July 2018 – 1st September 2018. Potential participants were identified and approached by CW-D, the project was discussed briefly and, if they continued to be interested, full discussion about the project took place.

4.4.5 Consent to participate

Following assessment of eligibility, the purpose and design of the study was explained to each potential participant. They received an "invitation to participate" letter and time was allowed for them to consider the study and ask any questions prior to completion of the consent form (Appendices 16 & 17). The participant was offered the option of arranging the interview on the day of attending the Late Effects Clinic, to reduce

inconvenience to them, or through a telephone interview (telephone interviews would have required the quantitative questionnaires to be completed and posted to CW-D). No participant requested a telephone interview.

Many participants wished to complete the consent form at the time of recruitment, therefore the consent form was completed and then reconfirmed at the time of the interview.

4.4.6 Interview method

Once recruited participants completed the three quality of life questionnaires prior to the face-to-face semi-structured interview. The participants were advised that the interview would last as long as they wished, however it would be no more than 60 minutes, allowing for a thorough discussion around the topic areas.

The topic guide focused on the following subject areas and additional questions were asked dependant on the responses from participants during the interviews or due to the analysis of all the previous interviews:

- Diagnosis and medical treatment to date
- Views on the care pathway
- Views on dental service and /or treatment received
- Feelings around dental treatment and advice
- Impact of dental treatment and advice – change in oral health behaviours, speech, function, appearance, quality of life, outcome of HSCT
- Oral complications pre assessment / during / following HSCT process

- Future views of dental treatment and oral healthcare

The topic guide used can be seen in Appendix 18.

4.4.7 The interviewer

Charlotte Wilson-Dewhurst (CW-D) was the sole interviewer for this study. Interviews occurred on specified sessions around her clinical timetable. She is a fully qualified and experienced dentist who has worked on the Special Care Dentistry Department at LUDH for 3 years and was in specialty training in SCD at the time of the study.

Potential participants who were assessed or treated by CW-D were excluded from this study as this was considered as a potential source of bias. Potential participants were made aware of CW-D's role as a clinician within the Special Care Dentistry Department.

4.4.8 Interview process

Interviews were recorded on a recording device (M Audio Microtrack II). Any additional information regarding difficulties in recruitment, need to stop the interview and participants becoming upset was noted in a separate field diary.

Participants were informed the interview could be stopped at any point without impacting on their clinical care. If a participant wished to withdraw from the study then their information and responses, up to that point, would be destroyed.

4.4.9 Data Analysis

Following the interviews the recordings were transcribed verbatim by CW-D. Thematic analysis was the method of choice for analysis of the

transcripts as it is more flexible and allows identification, analysis and informs reporting patterns within a data set (Braun and Clarke, 2006, Green and Thorogood, 2014a, Ritchie et al., 2014a)

Analysis occurred continuously throughout the study to allow emergence and identification of themes which were then were used as discussion points for other participants (Ritchie et al., 2014a).

Ideally recruitment continues for qualitative research until saturation is achieved. Saturation is the point where no new themes are emerging from the data (Green and Thorogood, 2014b, Ritchie et al., 2014b). However, within qualitative literature, saturation has different definitions depending on the author's own views. Some authors state that saturation is the point where no new codes or themes are emerging whereas others state saturation has been achieved if the participant has saturated their own narrative. Other authors have suggested that saturation is achieved when the theory under investigation is represented by the data (Saunders et al., 2018). Therefore, guaranteeing saturation has been achieved is arguably difficult and can depend on the definition adopted.

As a guide, a total of 37 allogeneic HSCTs occurred in 2016, therefore it was unlikely that the total sample for interviews, within the time available would be higher than 20 participants. In addition, Guest et al. found that, for in-depth interviews, all of the codes (and therefore themes) were identified within the first 12 interviews and so recommended between 6-12 interviews as an initial sample size (Guest et al., 2006). Given the difficulties in recruitment, the varied nature of patients receiving allogeneic HSCT and the

time constraints on the study it was difficult to be certain that saturation was achieved.

Key codes and themes were identified from the data by CW-D and these were subsequently reviewed by other members of the research team.

For the quantitative quality of life questionnaires, their individual scoring systems were used to quantify the data. Descriptive statistics were used to compare the data on advice from a Senior Biostatistician.

4.4.10 Ethical approval

Full ethical approval was gained for this study with HRA and Health and Care Research Wales (Appendix 1) see section 3.6.11 for further details.

4.4.11 Data management

The recorded interviews were uploaded on to hospital password protected computers and transcribed verbatim. Each audio file and transcription were assigned a unique identification and no patient information was included on these files.

For information regarding archiving see section 3.6.12.

4.5 Results

4.5.1 Data analysis

4.5.1.1 Thematic analysis

Thematic analysis is a widely used, flexible and substantive approach to analysing qualitative data, through identifying and reporting patterns or themes. It is often used within other qualitative analysis methods, however, it is argued that it can stand alone as an analysis tool presenting rich and detailed accounts of the data (Braun and Clarke, 2006, Ritchie et al., 2014a).

For this project a deductive semantic approach was undertaken (Braun and Clarke, 2006). The topic guide and the researcher's prior knowledge were developed from literary evidence, current expert opinion and practice. This in turn influenced the methodology and questioning during the interviews. Although, ideally an interpretive approach is suggested for analysis, the prior knowledge and professional status of the research team would have influenced the analysis and tailored participant responses to prior knowledge. The participants views and opinions allowed more meaning and context to be given to existing knowledge on this subject area (Green and Thorogood, 2014a).

Thematic analysis seeks initially to find codes, important words or fragments of text (fragment coding) of interest to the researcher, similar codes are then grouped into categories, allowing themes to be generated. A theme is an important element of the data in relation to the research question or participants' responses (Braun and Clarke, 2006, Green and Thorogood, 2014a, Ritchie et al., 2014a).

As stated by Braun and Clarke in 2006 there are six main stages to thematic analysis (Braun and Clarke, 2006):

1. Familiarising yourself with the data
2. Generating initial codes
3. Searching for themes
4. Reviewing themes
5. Defining and naming themes
6. Producing the report

4.5.2 Recruitment

Recruitment of this patient cohort was challenging as each patient had individual conflicting demands on their time. In addition, approximately 40 allogeneic HSCTs are completed by the Stem Cell Transplantation and Cellular Therapy Unit (CCC) each year, with some patients not surviving, presenting a small sample from which to recruit.

The Late Effects clinic within the Stem Cell Transplantation and Cellular Therapy Unit (CCC) is an outpatient clinic where adult patients who are 100 days post-transplant are reviewed. The clinic reviews patients who have had autologous or allogeneic HSCT in addition to those patients who have received other treatments for their haemato-oncology malignancy such as chemotherapy. The patients attending this clinic may have received their transplant within the last 100 days, or their transplant may have occurred over 2 years ago, but they still require follow up due to their haemato-oncology diagnosis or treatment history. Thus, the clinic presented a broad sample of patients of varying complexity and differing experiences.

Recruitment occurred over 8 clinical sessions, with 15 patients meeting the inclusion criteria for the study, 12 of these participants were interested in the study, with 7 confirming they wanted to take part and the other 5 patients wished to consider the study further in their own time.

A further difficulty experienced in recruiting participants to the study was arranging a suitable time to complete the interview. Although the patients had a booked appointment time, there was a fluidity to the appointment journey, which may involve additional procedures such as blood tests or treatments such as transfusion, therefore it was difficult for patients to anticipate at what point they would arrive on clinic or how long their consultation would be. For some patients, the interview was rearranged on three occasions because their consultant requested more tests, they didn't have a family member with them, or because they had other arrangements outside of the hospital. Given the number of appointments that they were required to attend, participants were reluctant to attend on a separate day. In the end, a more relaxed approach was taken and it was agreed with the participants that they would decide when the interview would occur.

4.5.3 Initial analysis

A total of 7 semi-structured interviews were completed within the time frame of this study. Data saturation is used within qualitative research to define the point at which no new themes are emerging from the data.

From the analysis of the 7 interviews no new themes were emerging at the last interview. Given the variety of individuals, treatment history, haemato-oncological diagnoses, patient experience, and difficulties in

recruitment, it was unclear whether data saturation had been fully achieved for this cohort of patients.

Four female and three male participants, were interviewed over a range of 13 minutes to 45 minutes. The average age of the participants interviewed was 44.3 years (range 27 years – 63 years) and their haemato-oncological diagnoses were that of Hodgkin's lymphoma (n = 1), acute myeloid leukaemia (AML) (n = 4) and myelodysplastic syndrome (MDS) (n = 2). During the interviews, the interviewer made minimal field notes of any further information stated outside of the interview.

Following completion of the interviews, the recordings were transcribed verbatim by CW-D. The transcriptions were completed by CW-D allowing her to be fully immersed within the data to aid in its analysis. It was also felt that transcribing the recordings was an effective method for CW-D to debrief, given that some of the interviews were difficult in their emotional impact on the interviewer. The transcriptions were then confirmed against the recordings as being accurate, by re-listening to the recording at a different period of time. An example of a transcribed recording can be seen in Appendix 19.

The transcripts were read prior to analysis to increase the depth of understanding of the data. The data was then read initially line by line and coded. Fragments of the data were also coded if it was felt that this allowed the code to be more robust. The transcripts were analysed, where possible, prior to completing the next interview to allow the concepts to be considered in the interviews as they progressed.

The initial codes and categories were reviewed and discussed with supervisors and qualitative researchers involved in the project (ST, RH and LL) to ensure there was agreement prior to formulating themes.

Once coded, the codes were grouped into categories and then into themes. This was completed initially on a Microsoft PowerPoint® document (see example in Appendix 20) and then as a paper-based exercise. Nvivo® computer software (QSR International) was trialled, however, the researcher did not feel, personally that this allowed for a good visual representation of the data. The data was then presented in tables to allow collation of the codes, categories and themes.

The data analysis process and tables can be seen in Appendix 21 (posters created and tables).

4.5.4 Identification of themes

Four main themes emerged from the data:

- Preventing transplant related complications
- Patient experience of the care received
- Consequences of medical management
- Psychological impact of treatment

A schematic diagram of the main themes identified can be seen in Figure 4.

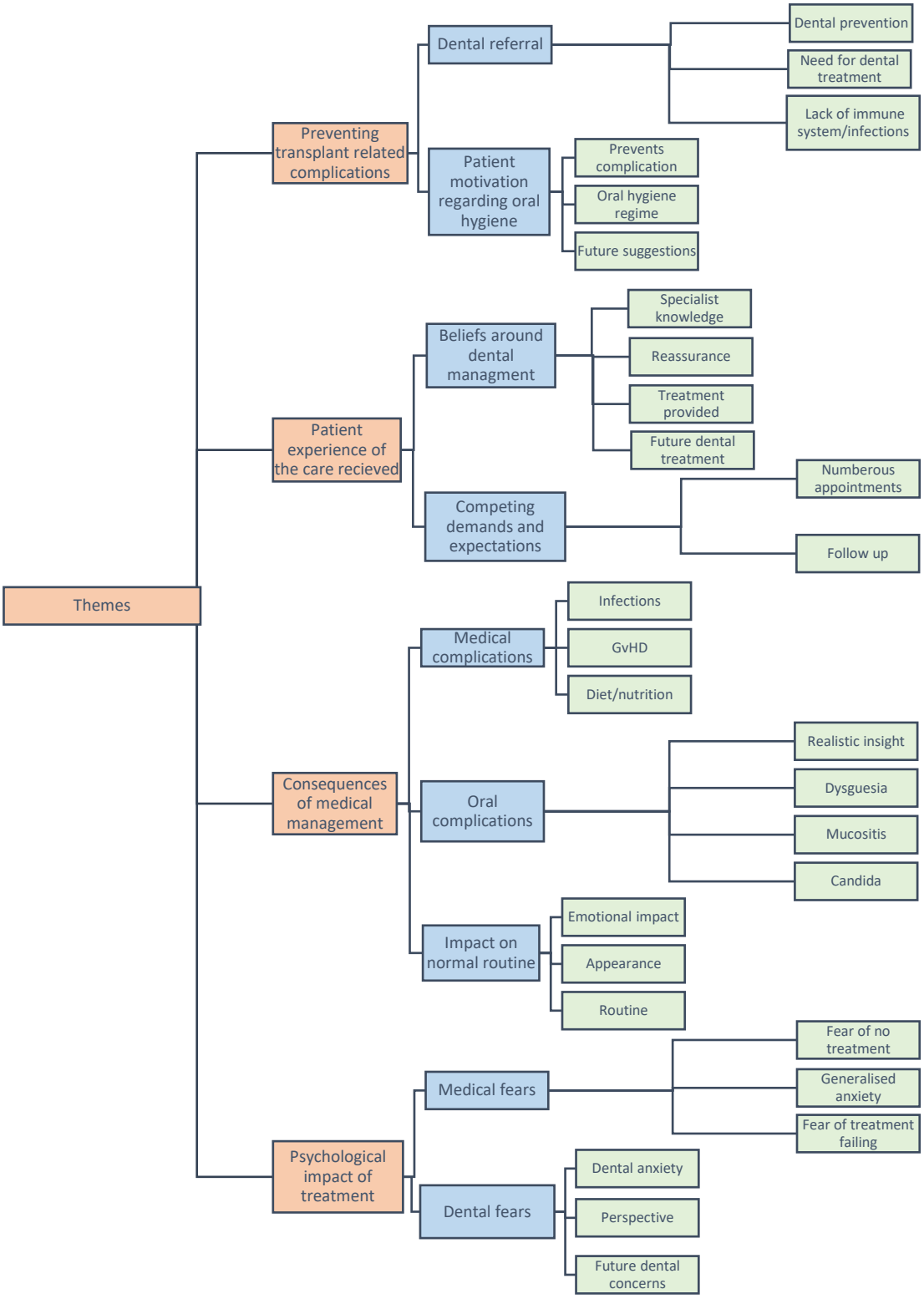


Figure 5: Schematic representation of the main themes identified through thematic analysis of the data

4.5.5 Preventing transplant related complications

Participants alluded to the fact that a dental assessment and necessary treatment was required to prevent complications during and following the HSCT process.

4.5.5.1 Dental referral

The need for dental referral was discussed during the interviews. The participants appeared to have been informed by their specialist medical team about the referral and the reasons for it. Some of the participants had previously had medical interventions such as chemotherapy for breast cancer or a hip replacement and so had an understanding and previous experience of dental assessment and intervention prior to medical treatment.

Prevention and the need for good oral hygiene was highlighted together with the provision of dental interventions as two of the reasons for dental referral.

> "*…I had to have good dental hygiene, in case I needed any teeth removing or if there was any problems that could, they could see before…*" P2 Female

> "*…errrm and then obviously for preventative care during the transplant*." P3 Female

> "*…I thought it might have been in case any of my teeth or fillings came out during any procedures…*" P5 Male

In addition to provision of treatment and delivery of prevention advice, participants were aware of the impact of the conditioning and transplant on their immune system and therefore the need to avoid or treat potential

sources of infection in order to reduce the risk of complications. Some of participants identified the mouth, teeth and gums as a potential source of infection and the impact an infection would have during transplant and so this highlighted the importance of the dental assessment.

> "*…but no it was explained to me that I would lose my immune system so basically I was open to to anything and one of the last things they wanted was any hidden germs or anything lurking in my body and obviously the mouth is one the places that things can lurk and go undetected*" P5 male

> "*…just to just to check off another box in case that you know I had the infection in my gum you know maybe I had a dodgy tooth for instance and could of easily got an infection in there once me immune system was down so that's what I assume is you're just covering all the corners*" P6 male

> "*…obviously they're checking for any infections or problems before the transplant so that can be avoided errrm coz obviously you've got no immune system when you're having your transplant so having something that bad with no immune system must be awful and then obviously all the medications and treatment you've had can affect your teeth…*" P7 female

4.5.5.2 Patient motivation regarding oral hygiene

There is evidence within the literature that good oral hygiene can reduce the oral complications faced by patients undergoing HSCT, particularly the duration and severity of mucositis (Gürgan et al., 2013).

Participants identified the need for good oral hygiene to reduce the severity and complications particularly presentation of ulcers.

"*…people who've had really really bad problems with ulcers, so I was quite lucky, but I was quite methodical at keeping my mouth clean. So I think that I help myself so yeh*." P1 female

"*…when I'd had my breast cancer and me chemo, it really affected me mouth then, I had a lot of mouth ulcers, so I knew what was coming like this time, so I was a bit paranoid over, straight away I asked for mouth wash and I was using it probably about 5 or 6 times a day, just to keep my mouth clean*." P2 female

"*…no do everything, they the nurses and doctors tell you you know they do tell you to do as you know oral hygiene is a big thing and it certainly helped me with not having as many blisters and pain I suppose than other patients that were admitted at the same time*" P6 male

In addition, participants highlighted the importance of trying to continue oral hygiene regimes as normal during the transplant process, however highlighted the fact that on some days they felt too tired or unwell to brush their teeth.

"*…brushed them in the morning but at night but I you know I was trying to do it in the middle of the… and I just couldn't be bothered but I think you should force yourself really to do what you'd normally do…*" P4 male

"*…pain wise no... errm no I was probably, I took me time I got a baby brush a baby toothbrush... so it was I brushed quite gently as I say took my time and had no problems*." P6 male

"*No issues with brushing my teeth...errrm I think a couple of days I probably didn't brush em in the morning because I just couldn't physically couldn't get out of bed… But as soon as when my mouth was hurting I'd probably like make the effort to swig some mouthwash or something yeh*" P7 female

However, other participants felt that during the post-transplant period their priorities changed and therefore maintaining their oral hygiene regime became less important to them.

"*…you're given advice about your teeth and all of a sudden you're in intensive care and you think you're going to die so throwing some toothpaste on your pearly whites doesn't sort of... it's not up there really is it?*" P5 male

"*I felt I was going to die and that's before I had me bad spells, that was just me that was just the way I felt I just thought I'm not going to pull through this and I was aware that err I was aware the dental hygiene wasn't being done I was aware that I wasn't cleaning my teeth but I didn't get like any bad breath or anything it was strange. I didn't, my mouth didn't feel yacky*." P5 male

"*…there are going to be parts of transplant like when you've melphalan, you physically can't brush your teeth because your skin*

falls off like it... (Laughs) like you're going to end up with a toothbrush full of gum.” P3 female

Although the some participants felt that the oral hygiene advice was adequate, others felt that changes to provision of oral hygiene advice were necessary, as patients undergoing HSCT become saturated with information with regards to their condition and treatment. Suggestions around provision of written advice, a personalised prevention plan that could be made available on the ward and involvement of relatives in providing oral hygiene, along with highlighting any issues with the mouth to nursing staff were made to improve the service.

“*…actually write it down, like a treatment plan for each person, even if you could just speak to them and say look focus on this, this and this… if they could write it down maybe do a note sheet for in each of the transplant rooms because your head is that muddled by everything that your being told in the run up to transplant you can't remember ANYTHING*” P3 female

“*…just sort of saying there are going to be times when you can't do it but just in the days afterwards make sure you're really careful, and make sure you notify the nurses if you think there is anything amiss*.” P3 female

“*I’d advise anybody to certainly try even if it comes down to something I didn't do if you can get your partner or one of your family to clean your teeth for you*.” P5 male

4.5.5.3 Theme summary

Generally, participants were aware of the importance of the dental referral, assessment and treatment in order to prevent infection. Additionally, participants recognised how good oral hygiene can prevent oral complications, namely ulcers, through the transplant process. Trying to continue normal regimes was important to these transplant patients, and was highlighted in the efforts made by participants in attempting to carry out their oral hygiene regime, despite feeling tired or unwell as a result of the transplant. Participants also recognised how their priorities changed during the transplant process and, therefore oral hygiene may not be the most important factor in recovery. Further developments to the service in the provision of written oral hygiene advice would be helpful to both patients and their relatives along with ward staff.

4.5.6 Patient experience of the care received

In all healthcare settings, understanding a patient's experience of a service is necessary in order to improve patient satisfaction and to implement changes (Batalden and Davidoff, 2007). There are often differences seen in the service provided and the expectations of the patients who access that service. For these participants, their experience of the care pathway and their expectations of treatment were explored.

4.5.6.1 Beliefs around dental management

The care pathway between the Stem Cell Transplantation and Cellular Therapy Unit (CCC) and the Special Care Dentistry Department was established in 2013 to enable patients to have a dental assessment and any necessary treatment prior to their HSCT, for emergency situations during the

transplant process, and for further dental review following transplant and recommendation regarding ongoing oral care and oral care provider.

There was a general feeling amongst the participants that being referred to the dental hospital meant seeing a dentist with increased specialist knowledge and experience. They felt that their diagnosis and its impact, along with the medical treatment they had received, was understood by the dental team with regard to the complications they might face, such as risk of infection and bleeding tendency.

> "*…fine it was erm good really when if you go to your own dentist you got to do all the explaining of I've had this I've had that, whereas going to the Dental they know all the case notes and they know what you've been through .. and ... what's happening so it's much much better*." P1 female

> "*…even my regular dentist didn't really understand what a stem cell transplant was and you're kinda sat there going... I've got to explain all this and then he's going to go digging about in my mouth unless I I I wanna feel comfortable that he knows just as well as I know, what it entails and how easy it is to get a nasty infection and that sort of thing...*" P3 female

> "*…It was helpful to see the Special Care Dentistry to be honest I think more than anything, as a transplant patient... I personally was terrified of going anywhere that might not... understand my condition and might not understand how clean it needs to be and how careful they need to be." P3 female*

Participants viewed seeing a specialist dental team for a dental assessment prior to transplant as reassuring and also found the attitude of the staff who saw them likewise as reassuring. They appreciated that in the early days of diagnosis and treatment having this link meant that the service was more direct in terms of communication and referral.

> "*I remember being quite happy because... (Cough)... somebody that I'd like gone through my journey with, who's no longer with us now. I remember him, bless him, he was terrified of the dentist and he had to go and have a load of teeth out before... we both like came here. So, and I was like breathing a sigh of relief because I didn't have to have anything done.*" P2 female

> "*...it's been relax...fairly relaxed in there and errr been seen to quickly and that and err no I haven't had any sort of problem you know... you know and everyone's sort of nice just... talking and joking away with you but I suppose to relax you like which you want (laughs) don't you, when you're feeling a bit worried about it*" P4 male

> "*I think the link between the Dental Hospital and here I think that link might be more direct and stronger than when it goes outside. So, every patient in the early stages is coming from one place not like there's a dentist in the Isle of Man, there's a dentist in Wales, Manchester, Wallasey it's all coming from one place that would be the benefit in the early days.*" P5 male

Amongst the participants, there was a variety of expectations of the dental treatment provided. The dentist's aim of treatment prior to transplant is

to allow the patient to be as dentally fit as possible in the time available, therefore the treatment plans prior to transplant include extractions, basic restorations, plus periodontal treatment aiming to see the patients following transplant to complete the more advanced work. Aesthetic concerns were highlighted by participants, with the provision of composite restorations, whitening treatments and provision of dentures being important to them. Expectations of treatment modality were explored particularly with participants who had dental anxiety. These participants attended expecting dental treatment under general anaesthetic but received their treatment under local anaesthetic.

> "*I had this idea in my head that after me transplant that I would go back to the dental hospital and I would have some like magic... treatment (laughter) on me teeth, and it would make them sparkling white, but that never happened…*" P2 female

> "*…some that would have to come out but probably the worst thing is, you know errr I think well what I thought was like there not coming out straight away and that and and I was hoping I would be knocked out…*" P4 male

A contrary view was that the dental treatment received was not a priority during the transplant process, however, they could see its importance in being a part of the process in the work up to HSCT.

> "*I think visiting a dentist to get your mouth checked out doesn't come very high on the scale of when you're having chemotherapy although looking back... err it is an important part of the procedure, at*

the time when you're putting it I don't think it comes in the top three but it is like I say an important part." P5 male

Together with the dental treatment received, there was a range of expectations as to where participants should receive their dental care post-HSCT. Current guidelines suggest that, for 1 year following HSCT, patients should be reviewed either within a secondary care setting or within primary care with close liaison with specialist dental services. However, this decision would be governed by the patient's medical stability and haematological status (British Society of Disability and Oral Health, 2012). Some participants were happy to be seen at the Dental Hospital but were accepting of the fact that they would be discharged in the future.

"*I'd like to think they'd carry on seeing seeing me but errrm we'll just have to wait and see.*" P1 female

"*Well... I think in a few ways it would be a lot better if I could just go to somebody in Southport, but I'm quite happy at the moment coming to the Dental Hospital.*" P4 male

"*it all goes hand in hand with my condition like when my platelets are low I quite understand that I've got to stay away from things that are sharp and dentists tend to use a lot of sharp things... err but I think once I think once your platelets are back ok, I personally don't see why your own dentist can't treat you… I really can't see the difference between your own NHS dentist treating you and coming to a Dental Hospital, I see that the err tooling is the same, the*

procedures are the same the only thing that changes is me is my platelet level" P5 male

4.5.6.2 Competing demands and expectations

Participants highlighted that patients who were receiving treatment for Haemato-oncological diseases often needed to attend multiple appointments, including chemotherapy and radiotherapy treatments, regular appointments for blood tests and in-hospital stays prior to, during and following transplant. This often meant that they had conflicting demands on their time.

"*had a course of radiotherapy.... it came back... so i had a transplant, using my own cells...erm stem cell transplant in between having chemotherapy stuff... i relapsed and it come back in other parts... erm... so they decided that it would be best if i had a donor transplant.... so errm I had months and months of chemotherapy*" P1 female

"*yeh so it's it's my second anniversary of being diagnosed tomorrow so I've spent 53 weeks in hospital that was up to May so it's still luckily only 53 weeks now but that's if you take the anniversary tomorrow that's over half of my time I've spent in hospital very very ill*." P5 male

"*the 8th 9th 10th and 11th was radiotherapy, total body irradication errm twice a day, on the 11th I came back to the Royal and errrm on the 12th I had err I think two doses of chemotherapy and then the 13th I had errrm I think I had fluids and then I think the 14th I had the stem cell transplant.*" P6 male

As well as attending their regular treatment appointments, the patients were also required to attend specialist appointments to assess their cardiac and respiratory function, for psychological support and for a dental intervention.

"*…coz obviously they wanted to harvest my eggs before I went into transplant and what have you and... They wanted to do lung and liver and all your like different function tests*." P3 female

"*I think it was only the ones really all the other were sort of connected you know one way, you know like counsellors even or there was this one, I don't know whether she was a psychiatrist or that I saw a few times.*" P4 male

"*…you know for your breathing for your lung, I had to have like a breathing test and then a errrm heart monitor as well... yeh before my transplant*" P7 female

In addition to attending appointments, these participants felt saturated with information, regarding their diagnosis and treatment.

"*…what people have said to you is just unreal you're learning stuff about your condition, you're learning stuff about your diagnosis, about your treatment every minute that you're in this hospital.*" P3 female

Participants highlighted the struggle they faced to attend appointments or to remember the reason for the appointment. In certain cases, it was not possible to complete the dental treatment prior to the HSCT as the need for

the HSCT was more urgent than the dental treatment itself, or if the dental assessment appointment was too close to the transplant date.

> "*…Errr to be honest there was that much going on at the time it wasn't sort of... it was just... there were that many different appointments I think you kinda lose track of what you're going to appointments*" P3 female

> "*I think I should have had some stuff.. some work done before me transplant but I always thought for some reason, someone said the dentist had broke her leg and then it just got too close to having me transplant*" P4 male

> "*It was just before my transplant, so I went I think it was a week before I had my transplant yeh…*" P7 female

Participants highlighted they felt they had a lack of knowledge regarding what dental treatment they required or when it should take place, this was both in regard to dental treatment prior to and following HSCT.

> "*…oh no we're taking your wisdom teeth out today and I was like, well I haven't booked any time off work coz I didn't know you were going to do that, so can we not (laughter)... and... They're still in there but they've done alright*" P3 female

> "*I needed a errrm a filling. Errm it's like coated but he said he could like do a filling for it when I after my transplant, but I've not heard anything back yet. I've not had another appointment to do that*" P7 female

In addition, following HSCT, participants felt that it was unclear as to how they accessed returning to the Special Care Dentistry Department for a review or to complete treatment, leading to delays in their accessing dental care.

> "*I think the only improvement would be with the follow up that I had to, I did have to chase that errm, coz I asked a few times at errm... I think I asked in clinic upstairs and I asked a few times at my appointments, like my consultants appointments, and it was months before it was sorted and like in the end I sort of had to push for it*" P2 female

> "*No I should have came back a lot sooner but I don't know what happened, I don't know whether it was my fault not following it up with yourselves probably I think it was my fault for not phoning coz I think I had a we arranged err a filling I got an appointment letter in the post but I was having me transplant at that time*" P6 male

4.5.6.3 Theme summary

Overall, participants felt reassured by the link between the Special Care Dentistry Department and the Stem Cell Transplantation and Cellular Therapy Unit (CCC), as they felt the dental clinicians they saw had specialist knowledge and experience of treatment for patients with Haemato-oncological diagnoses. However, many patients understood that once their haematological values were stable following transplant then they could be seen by their own GDP, closer to home, whom they may have known for years and in whom they had developed trust and rapport.

Participants highlighted that more information was required, in different formats, to explain the dental treatment that could be provided and the process of accessing dental care following transplant in order to manage expectations and prevent delays to treatment. In addition, careful liaison is required with the Stem Cell Transplantation and Cellular Therapy Unit (CCC) to allow ample time for patients to have an oral assessment and ideally have any necessary dental treatment prior to transplant.

4.5.7 Consequences of medical management

Following HSCT patients are likely to develop complications that can impact on their recovery and survival. The complications can occur directly following transplant or have a delayed presentation.

4.5.7.1 Medical complications

The treatments required to manage or cure haematological malignancies; chemotherapy, radiotherapy and transplant results in patients becoming immunosuppressed and thus increasing their susceptibility to infections. Participants within this study eluded to the infections they experienced following treatment, resulting in further hospital stays and additional treatment for the infection.

> "*…then in the October so 10months later I got sepsis and pneumonia, errm and ended up in intensive care at the Royal and nearly died.*" P2 female

> "*…I was only out for a month and had to go to Arrowe Park for a week err I picked up an infection so unfortunately that's the way I and other patients are*." P5 male

The infections experienced by participants were a combination of viral, bacterial and fungal organisms.

"*…prothioconazole stuff like that which, that's not nice, errrm but that was for a fungal lesion on my lung, and then I got a virus and was on... Ribavirin errrm so I've had that in tablet form and in... the nebulising form, which is really really unpleasant*" P3 female

Graft versus Host Disease (GvHD) is an early and late complication of an allogeneic HSCT. Presentation of GvHD after 100 days being classified as chronic GvHD. Participants within the study described how the GvHD affected their skin, bowels and mouth. One participant experienced a particularly severe form of GvHD affecting his bowel which impacted on his nutrition and required an extended stay in hospital following his transplant.

"*…I had the most horrific rash from here right up and all over my head and it was just like really really itchy, so that's when they started me on the steroids.... and then I had it in my.... tut... bowel as well... erm so that was probably connected to why I was not eating very much and had no appetite*" P2 female

"*I remember it started inside me mouth a bit milky looking, me lip was a bit purple and milky looking just the bottom one the top one seemed alright*" P4 male

"*GvH of the mouth, GvH of the skin, GvH of the eyes, although horrible and uncomfortable won't kill us, it's the GvH of the gut that apparently is the killer…*" P5 male

Receiving good nutrition directly following HSCT has been shown to improve recovery (Espinoza et al., 2016). Patients are encouraged to eat as normal, however, some require supplemental nutrition including nasogastric feeds, total parenteral nutrition (TPN) and build-up drinks. Participants discussed the issues of having a lack of appetite as a consequence of feeling depressed, others explained that having a sore mouth and lack of taste reduced their appetite.

> "*…the smell of the food was just knocking me sick and I don't, I don't know whether, thinking about it now whether I was just a bit depressed about it all and that was my way of dealing with it, by not eating...*" P2 female

> "*Oh I didn't eat for 2 weeks, they wanted to put a tube in and all sorts but I think that was infection and the fact that my mouth was red raw...*" P3 female

> *"…*errrm I could eat quite a lot at the start of it all while my taste was gone but towards the end… I err couldn't eat much" P6 male

The majority of participants were accepting of the need for supplemental nutrition, however, some found the thought of having a nasogastric tube distressing.

> "*…so... .... I know it sounds really strange of all the things they've done to me the one thing that really really puts me off more than anything is them putting a tube down my nose, I just can't deal with it*" P3 female

"*…you've got to get nutrients in if you don't say you go off your food and errr if you haven't got the tube up your nose you're not getting any nutrients you'll be in longer and as soon as they said that you know I just wanted to get out so I say I agreed to it then*" P4 male

"*I had numerous NG feeds yeh, err there came a point where I was that bad with the graft versus host of the gut that I was stopped fed by NG… I was fed with what they called errm TPN… fed direct into the vein because my gut was that affected they didn't want to pass anything through*" P5 male

"*…they did try and give me that several times and I I said I said no but every time, I just tried to force down which I did yeh... it's just something that I didn't like the the look of really it seemed quite uncomfortable errrm so yeh I was quite happy trying to force it down me*" P6 male

4.5.7.2 Oral complications

Oral complications are frequently associated with HSCT. This has been explained by sensory changes caused from the Haemato-oncological malignancy itself, a reduction in the number of taste receptors, and the use of chemotherapy drugs resulting in neurotoxicity and xerostomia, leading patients to experience dysguesia, mucositis, ulceration and xerostomia (British Society of Disability and Oral Health, 2012, Meirelles and Diez-Garcia, 2018). In addition, the susceptibility to infections results in opportunistic organisms, particularly candida, presenting in the mouth (British Society of Disability and Oral Health, 2012).

Participants within the study had insight into the oral complications that they had experienced. They were aware that they would be likely to have a sore mouth and taste disturbances and this information was discussed prior to transplant and they were able to place their experience of oral complications into perspective in the context of the rest of their treatment.

> "*If you're outside of transplant and your mouth was that bad, then yeh that would really suck but I think in the greater scheme of things when you're in transplant you kinda have bigger fish to fry…*" P3 female

> "*Awful, it wasn't as bad as I expected because people had told me like the doctors the dentist as well, that like you're going to get a really sore mouth, so it wasn't as bad as I thought*" P7 female

Dysguesia, or taste disturbances, was a complication that many of the participants experienced, and this, along with the difficulties in eating, was a lasting memory of that period.

> "*…the weird thing, I'd lost all taste in my mouth for the best part of 2 weeks... errm... I couldn't taste anything, like I had a relentless...and that stuffs just pure fizz but I was like, it's got a fairly strong taste... nothing. The only think I could taste was Rubicon Mango and I hate that stuff.*" P3 female

> "*…me taste buds must of went for maybe, I think a good month, good month or so errrm all I could taste was MacDonald's cheese that was the that was everything, everything tasted like MacDonald's cheese believe it or not so ummm very strange…*" P6 male

A participant described how he was advised by other patients on the ward how to combat the problems with taste that he was experiencing.

"*…somebody said to me if you drink oxo or Bovril you don't get the metallic taste and another one apparently is pineapple*" P5 male

Participants' experience of mucositis was not as clear, as they mainly described having a sore mouth or their experience of ulceration. Again, mucositis experience was a further factor that impacted on nutrition and ability to eat, throughout the transplant process resulting, in certain cases in nasogastric feeding.

"*…then of course on top of that you've got the soft tissue break up... the skin splitting in the mouth and everything yeh... no not a good time that*" P5 male

"*…errrm I can't remember what it was called now, but you get like a horrible like foam on your mouth and yeh a really sore mouth, it was I couldn't eat a lot really no*." P7 female

Another participant described experiencing a candida infection, however, considering the other complications she experienced, she was not surprised to contract an oral infection.

"*... no I got oral thrush I think twice and had to have nys... nystatin, errm but that's pretty sort of common coz it's... I mean I got fungal infections in my lungs so... it would kinda come hand in hand that you might get one in your mouth... so... but worse things have happened so...*" P3 female

4.5.7.3 Impact on normal routine

Participants discussed, in addition to the medical complications they experienced, how the HSCT process impacted on their daily life. In particular, patients highlighted the change to their appearance through weight loss and hair loss, as impacting on their mood.

> "*…went down to that weight I just would look at myself and it was just awful, you could just like feel my bones and yeh...*" P2 female

> "*…me hair as well errm emotionally I think it was quite... quite depressing errm having no hair whilst being wheeled through the hospital and people starring at you errrm that was quite quite upsetting actually especially when everyone's looking at you err in that your feeling quite quite sick so for everybody to see*" P6 male

Their increased risk of bleeding and susceptibility to infection impacted on normal routines such as shaving. Participants were advised to use electric shavers to negate this risk.

> "*…and I used an electric shaver if I needed to shave*" P6 male

In addition, a participant explained how her fear of contracting an infection influenced her interaction with customers at work.

> " *…haven't been facing patients, up until recently because of the infection risk, obviously my boss didn't want me, getting an infection either so they've been really careful about not wanting to put me on the shop floor…now I can face some patients that come in, I'm just fairly picky about who.*" P3 female

The emotional impact that the HSCT had on patients both during the transplant process and after was described. It was explained that the impact was not only on themselves as the patients, but other members of the family if the patient was unwell.

> "*…three possibly four occasions where they've nearly lost me, err you know it's not just me it's the family as well you know the wife getting phone calls at 2.30 in the morning saying you need to come over as soon as possible*." P5 male

The feelings of friendship formed with other patients undertaking the transplant process was described and how patients may feel guilty for surviving when others have not.

> "*…you're then hospitalised for seven months and you come into clinic and you start asking about people who you haven't seen and then you find out that they've passed away whilst you've been in hospital. Errm it makes me feel guilty, I feel very emotional, and I think why me, why how have I survived, and these other people haven't survived and it's a real err I say eye opener it makes me feel like I say sometimes guilty that I'm still here*" P5 male

4.5.7.4 Theme summary

Participants are generally aware of the medical consequences of the HSCT and accepting of them as an outcome. An interesting finding from participants was the reluctance to have NG feeding, even though the evidence suggests that supplemental feeds improve recovery and decrease the duration of the initial hospitalisation (Espinoza et al., 2016). There was

only one participant in this cohort who had severe cGvHD which affected his bowel and significantly impacted on his recovery due to the issues of malnutrition. Taste disturbances were the most frequent oral complication described and the majority of the participants could remember their taste changing and the impact that had on how they felt about eating. There is a continued emotional impact of the treatment following transplant with participants reporting anxiety with regards to contracting infections or having guilt around surviving.

4.5.8 Psychological impact of treatment

Patients are confronted with numerous stressors throughout their HSCT journey which can have a significant psychological and emotional impact. In this study, participants described their feelings and emotions with regard to their medical treatment, and the dental treatment they received.

4.5.8.1 Medical fears

Throughout the interviews participants described their anxieties around their diagnosis, the treatment they received, and the appointments they needed to attend.

> "*So, you're kind of scared of your own shadow…*" P3 female

> "*Anxious, I get anxious with everything though, every appointment yeh*" P7 female

A participant explained that even now, 6 years post-transplant, she is still conscious about infection risk in her day to day life, including seeing clients at work.

> *"…I'm still like OCD about clean stuff (laughs)*" P3 female

In addition, participants explained their concerns regarding the often lengthy wait for a suitable donor to be identified. They explained how this often led to them having further chemotherapy treatment which resulted in experience of infections and other side effects alongside prolonged hospital stays.

> "*Waited on the register again, couldn't really find anything.... got to October really started to panic coz I'd had some really nasty infections and been in hospital pretty much 90% of the time*" P3 female

Another patient explained how he wished he had been given more information about the transplant process and the possible complications, prior to transplant, to help reduce his anxiety. He eluded that this information would be helpful from a patient's perspective.

> "*…more advice prior to the transplant would have been better for peace of mind, obviously it's quite nervous for anybody to have such a erm such a treatment for something like that a transplant err I think any advice would have been great, something to settle the nerves so yeh*" P6 male

Many of the participants had experienced multiple different treatments prior to their HSCT and, for most, having a HSCT was the only option for recovery. Participants described how some chemotherapy treatments made no impact on their disease whilst others explained that they has been in remission but relapsed.

"*…I been on lots of different chemotherapies, coz each one from the beginning of this didn't work... wasn't making any difference*." P1 female

"*…then I was told that I had no option other than the stem cell transplant, otherwise.... I wouldn't get better*." P2 female

"*…when I was in remission for about a year and a half, then it comeback and I relapsed in June 2017 which then meant that I had to have a bone marrow errrm transplant*" P7 female

One participant described his fear of relapse, now that he is post-transplant as he does not feel he could undergo the necessary treatment for a second time.

"*I've... really been through the mill and at times I've thought you know I wasn't going to pull through. And I'll be honest now I've said to a couple of people I honestly don't think I could go through that again, I don't think my body could go through that again, if I was to have a relapse I don't think I'd pull through it, I honestly don't think I could go through what I've been through*" P5 male

4.5.8.2 Dental anxiety

Further to the anxiety regarding their medical care, this cohort of participants reported feelings of anxiety in regard to attending for their dental assessment appointment, its impact on their medical care, and their feelings around the dental treatment required.

"*…yeh I mean no saying that I'm never I've never been comfortable with dentists err its needles I suppose it's not the best are they so no*" P6 male

"*…touch wood I've always had quite good teeth anyway, I don't like going the dentist obviously who does but errr I was ok yeh. Bit nervous had to have like an x-ray and stuff but yeh fine…*" P7 female

A participant described how his dental phobia had developed since his wife passed away. Since this time he had not accessed dental care and so felt anxious regarding his assessment appointment in Special Care Dentistry as he knew that dental treatment was required.

"*Like from 2006, I just never went the dentist, and I knew things were getting more, were getting worse, there was times where I said about forcing myself to go*" P4 male

"*Oh he'll have to be referred to the Dental Hospital... and I was a bit nervous at times about going but because everything they've done to me in here I've never had a problem with at all*." P4 male

Other participants explained their dislike of dental treatment, however, understood why a dental assessment and treatment was required prior to transplant and therefore viewed the dental aspects of care as part of the process.

"*Well I don't love them (laughter) but no it's fine*." P1 female

"*No the hospital have done worse to me so... I'm not too keen on that drill but other than that... it's alright*" P3 female

"*It didn't bothered me to be honest because I saw it as part of the process… It's like building the house you have to have the foundations in place before you lay the bricks and I just saw it as part of the process*" P5 male

Some participants did not receive their dental treatment until after the HSCT, however, felt that their views on dental treatment had changed due to the experience throughout the transplant process.

"*…like I say bone marrow things done and all that you just realise your teeth is just the same really you know it should be nothing really like… I always think I'd be fighting with the dentist, you know struggling with him like and err but like I say I was relaxed when I got in the other week and I think it's probably better for me being about another year, you know you can set your mind to it and you just realise it's nothing should be nothing really.*" P4 male

"*…it's changed from my experience with the stem cell and the amount of needles that you go through having that experience, so I think coz I had a bit of a phobia before this with needles, I think that's maybe helped me going the dentist a bit more*" P6 male

Alongside dental anxiety around dental treatment, participants expressed future concerns about their dental health and dental appearance from the effects of the medical treatment they have received.

"*I do worry about me teeth, because you know my gums are receding so I you know I worry about all that…*" P1 female

"*…that was one of me main worries I don't want sorta like gaps in me teeth*" P4 male

"*errm I was just worried a bit about you know in the past I've used the mouthwashes and my teeth's gone a bit yellow*" P7 female

4.5.8.3 Theme summary

Unsurprisingly, participants expressed feelings of concern and anxiety around their medical diagnosis, treatment and ongoing management. For many participants, the treatment required is complex and not always successful at inducing remission; necessitating the need for further interventions such as further infusions of stem cells, treatment for infections and treatment for GvHD. Such complications result in prolonged hospital stays and continued high frequency of medical appointments. Within the general population, dental anxiety is common and therefore the requirement of a dental assessment in the medical management for these patients could be seen to be overwhelming (National Health Service, 2009). However, many of the participants in this study demonstrated a realistic mind-set towards dental treatment, as it was not comparable to the medical management they had experienced.

4.5.9 Quality of life

Prior to the semi-structured interview participants were asked to complete three quality of life questionnaires. A full description of the quality of life questionnaires (Appendices 9, 10, and 11) used can be found within the methodology in Section 14.4:

1. FACT-BMT (Functional Assessment of Cancer Therapy – Bone marrow transplantation) (Appendix 11)
2. Lee cGvHD symptom scale (Appendix 12)
3. OHIP-14 (Oral Health Impact Profile – 14) (Appendix 13)

The questionnaires were scored at the time of the interview and, if relevant, were used within the interviews to allow for an increased depth of information.

Table 41 shows the demographics of the participants included in this study along with the overall results of the quality of life questionnaires.

	Gender	Age	Diagnosis	Year of transplant	FACT-BMT score	OHIP-14 score	Lee cGVHD score
1	Female	55.0	Hodgkin's lymphoma	2017	85.0	8.0	31.0
2	Female	44.0	AML	2016	88.0	11.0	14.0
3	Female	27.0	MDS	2012	108.0	24.0	34.6
4	Male	60.0	AML	2017	120.9	22.0	7.1
5	Male	63.0	AML	2017	76.0	13.0	34.3
6	Male	34.0	MDS	2017	100.0	21.0	19.9
7	Female	27.0	AML	2017	93.3	9.0	18.2
Average		44.3			95.9	15.4	22.7

Table 41: Overall results of the quality of life questionnaires

4.5.9.1 Fact-BMT quality of life questionnaire

Fact-BMT is a quality of life questionnaire used for to assess quality of life for patients undergoing bone marrow transplantation (McQuellon et al., 1997, FACTIT, 2010).

Since its development it has been used to assess quality of life across 5 domains:

- Physical wellbeing (PWB)
- Social and family wellbeing (SWB)
- Emotional wellbeing (EWB)
- Functional wellbeing (FWB)
- Bone marrow transplant subscale (BMTS)

The results of each question are scored individually on a scale of 0 – 4. Each section is then scored as per the FACT-BMT scoring guidance (available when a study is registered with FACT-IT). A total score is then derived by adding the scores of each section, providing a FACT-BMT total score. The higher the score the better the quality of life. The total score possible for the questionnaire is 148.

For these participants, the scores for each section and their total score are shown in Table 42.

	PWB score (28)	SWB score (28)	EWB score (24)	FWB score (28)	BMTS score (40)	Total
1	18.0	24.0	14.0	11.0	18.0	85.0
2	24.0	21.0	14.0	18.0	25.0	88.0
3	14.0	25.0	19.0	25.0	25.0	108.0
4	25.6	23.3	20.0	20.0	32.0	120.9
5	8.0	21.0	16.0	11.0	20.0	76.0
6	18.0	17.0	23.0	22.0	20.0	100.0
7	21.0	23.3	9.0	16.0	24.0	93.3
Average	18.4	22.1	16.4	17.6	23.4	95.9
Range	8.0 – 25.6	17.0 – 25.0	9.0 – 23.0	11.0 – 25.0	18.0 – 32.0	76.0 – 120.9

Table 42: Results of the FACT-BMT quality of life questionnaire

From the results it appeared that, on average, participants scored highest (higher quality of life) in terms of social wellbeing and emotional wellbeing.

On average, the lower scores were seen within the bone marrow transplant subscale which explored the additional concerns faced by participants. As can be seen from the results the wide range of responses confirming that the bone marrow transplant experience is different for each individual patient.

4.5.9.2 OHIP-14 quality of life questionnaire

The Oral Health Impact Profile – 14 is an adapted version of the Oral Health Impact Profile – 49 exploring the dimensions of oral health as first proposed by Locker in 1994, these include (Slade, 1997, Slade, 1998):

- Functional limitation
- Physical pain
- Psychological discomfort
- Physical disability
- Psychological disability
- Social disability
- Handicap

OHIP-14 uses these dimensions to evaluate the impact of the participants' mouth, teeth, and dentures on their daily life, including function, aesthetics, pain and emotional status. The questionnaire is scored from 0 – 4, where 0 refers to never having the experience of the issue to 4 where the issue is experienced very often. A high score suggests a worse oral health related quality of life. The total score of the questionnaire is 48.

The results for these participants can be seen in Table 43.

Generally, the participants had low scores in relation to their Oral Health Impact Profile indicating an overall better oral health related quality of life with

an average score for this cohort of 15.4 out of a possible 48. However, the range of responses varied amongst participants and this questionnaire was completed at one point in time thus no comparisons can be made. With regard to the question responses, the questions that received higher scores (thus indicating a poorer oral health impact profile) were question 5 and question 10. Both of these questions focused on respondents' feelings of self-consciousness and embarrassment in regard to their teeth.

	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	Total
1	0	0	2	0	0	0	0	2	2	0	0	0	2	0	8
2	0	2	0	1	1	1	0	0	0	2	0	2	2	0	11
3	0	0	0	2	4	3	1	1	2	4	3	2	2	0	24
4	0	3	2	2	3	2	0	1	2	2	0	2	3	0	22
5	0	3	0	2	2	0	2	0	0	2	0	0	2	0	13
6	0	0	0	0	4	4	0	0	2	4	1	1	3	2	21
7	0	2	1	0	2	2	0	0	0	2	0	0	0	0	9
Q. Total	0	1.4	0.7	1	2.3	1.7	0.4	0.6	1.1	2.3	0.6	1	2	0.3	
											Total average				15.4

Table 43: Results of OHIP-14 quality of life questionnaire

4.5.9.3 Lee cGvHD symptom scale

The Lee cGvHD symptom scale is used to assess the impact of the multi-organ manifestations of cGvHD on quality of life (Lee et al., 2002, Merkel et al., 2016). The questionnaire evaluates the impact of cGvHD across seven different domains consisting of thirty items:

1. Skin
2. Eyes and mouth
3. Breathing
4. Eating and digestion
5. Muscles and joints

6. Energy
7. Mental and emotional.

The participants were asked to limit their responses as to how they had felt within the last month at the time of the questionnaires being completed. The responses were scored from 0 (not affected at all), to 4 (extremely affected). The totals of each subscale were calculated and then linearly transformed to a 0 to 100 scale where 0 indicates that all answers were a 0 and 100 indicates all answers were a 4.

The results for this patient cohort are displayed in Table 44.

A summary of the total scores for each subset of questions can be seen in Table 45. For this questionnaire, higher scores represent a poorer quality of life with regards to cGvHD. Table 44 shows the total scores for each participant and the average score for each subset. As can be seen in Table 45, the total scores for each participant were quite low, ranging from 7.1 to 34.6.The average scores for each subset were low with the poorest quality of life in regards to cGvHD being seen in the subsets of “Energy” and “Mental and Emotional” where both subsets scored 39.3.

Overall, on viewing the results, it was apparent that the participants within this study generally reported having a good quality of life with regard to their bone marrow transplant, oral health and cGvHD symptoms.

Participant	P1	P2	P3	P4	P5	P6	P7
Skin							
a	1.0	0.0	1.0	0.0	1.0	0.0	0.0
b	3.0	1.0	1.0	0.0	2.0	0.0	1.0
c	0.0	0.0	2.0	0.0	0.0	0.0	0.0
d	0.0	1.0	2.0	0.0	0.0	0.0	0.0
e	0.0	1.0	3.0	1.0	1.0	3.0	1.0
Total for subset	4.0	3.0	9.0	5.0	4.0	3.0	2.0
Linear transformation	20.0	15.0	45.0	5.0	20.0	15.0	10.0
Eyes/mouth							
f	3.0	1.0	0.0	3.0	1.0	1.0	2.0
g	3.0	0.0	0.0	3.0	0.0	0.0	0.0
h	0.0	0.0	0.0	0.0	1.0	1.0	2.0
i	0.0	0.0	0.0	0.0	0.0	0.0	0.0
j	1.0	0.0	0.0	0.0	1.0	0.0	0.0
k	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total for subset	7.0	1.0	0.0	6.0	3.0	2.0	4.0
Linear transformation	29.2	4.2	0.0	25.0	12.5	8.3	16.7
Breathing							
l	0.0	0.0	2.0	1.0	2.0	1.0	1.0
m	1.0	0.0	1.0	0.0	2.0	0.0	1.0
n	4.0	0.0	1.0	0.0	4.0	1.0	1.0
o	1.0	0.0	0.0	0.0	1.0	0.0	0.0
p	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total for subset	6.0	0.0	4.0	1.0	9.0	2.0	3.0
Linear transformation	30.0	0.0	20.0	5.0	45.0	10.0	15.0
Eating							
q	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r	0.0	0.0	0.0	0.0	0.0	0.0	0.0
s	0.0	0.0	0.0	0.0	0.0	0.0	0.0
t	0.0	0.0	0.0	1.0	0.0	1.0	0.0
Total for subset	0.0	0.0	0.0	1.0	0.0	1.0	0.0
Linear transformation	0.0	0.0	0.0	6.3	0.0	6.3	0.0
Muscles/joints							
u	0.0	1.0	2.0	0.0	3.0	0.0	1.0
v	0.0	0.0	2.0	0.0	2.0	0.0	0.0
w	3.0	0.0	1.0	0.0	1.0	0.0	1.0
x	3.0	1.0	2.0	0.0	4.0	4.0	1.0
Total for subset	6.0	2.0	7.0	0.0	10.0	4.0	3.0
Linear transformation	37.5	12.5	43.8	0.0	62.5	25.0	18.8

Participant	P1	P2	P3	P4	P5	P6	P7
Energy							
y	4.0	1.0	4.0	0.0	4.0	1.0	1.0
z	2.0	1.0	4.0	0.0	4.0	3.0	1.0
aa	0.0	0.0	3.0	0.0	0.0	0.0	0.0
Total for subset	6.0	2.0	11.0	0.0	8.0	4.0	2.0
Linear transformation	50.0	16.7	91.7	0.0	66.7	33.3	16.7
Mental/emotional							
bb	2.0	2.0	2.0	0.0	1.0	2	0
cc	2.0	2.0	2.0	1.0	1.0	3	4
dd	2.0	2.0	1.0	0.0	2.0	0	2
Total for subset	6.0	6.0	5.0	1.0	4.0	5	6
Linear transformation	50.0	50.0	41.7	8.3	33.3	41.7	50

Table 44: Results of Lee cGvHD symptom scale quality of life questionnaire

	P1	P2	P3	P4	P5	P6	P7	Average
Skin	20.0	15.0	45.0	5.0	20.0	15.0	10.0	18.6
Eyes/Mouth	29.2	4.2	0.0	25.0	12.5	8.3	16.7	13.7
Breathing	30.0	0.0	20.0	5.0	45.0	10.0	15.0	17.9
Eating	0.0	0.0	0.0	6.3	0.0	6.3	0.0	1.8
Muscles/joints	37.5	12.5	43.8	0.0	62.5	25.0	18.8	28.6
Energy	50.0	16.7	91.7	0.0	66.7	33.3	16.7	39.3
Mental/emotional	50.0	50.0	41.7	8.3	33.3	41.7	50.0	39.3
Total score	31.0	14.0	34.6	7.1	34.3	19.9	18.2	22.7

Table 45: Summary of Lee cGvHD symtom scale quality of life questionnaire

4.6 Discussion

4.6.1 Interpretation of the results

Overall, the individuals within the study understood the reasoning behind a pre-HSCT dental assessment and the need to complete any necessary dental treatment prior to transplant. There was an awareness of the importance of good oral hygiene and how this needed to be continued throughout and following the transplant process. From the interviews, insight was gained into the challenges facing this cohort of patients, for example the need to attend multiple hospital appointments, difficulties carrying out their normal daily routines and the emotional impact of their transplant journey.

4.6.1.1 Preventing transplant related complications

In keeping with national guidance, all patients who are receiving a haematopoietic stem cell transplant, chemotherapy or radiotherapy for cancer treatment should receive a pre-interventive dental assessment, provision of dental treatment and preventative advice (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

The participants within this cohort were, on the whole, informed by their medical team (doctors and specialist nurses) as to the reason for attending the dental assessment and so viewed the dental assessment as part of the HSCT process. The individuals interviewed were informed that the mouth was a potential source of infection during the period of immunosuppression and understood that any dental pathology required treatment to reduce the risk of infection. A further qualitative study, completed in Brazil, also found that patients tended to only attend the dental assessment appointment as the request was made by the medical

practitioner thus it was seen as part of the HSCT process (Mendes et al., 2018).

However, one of the individuals within the cohort of the current study gained her knowledge from previous health care interventions. The individual had received a dental assessment prior to chemotherapy to treat breast cancer in 2011. During this episode of chemotherapy she experienced severe oral ulceration and was therefore aware, ahead of her HSCT, of the importance of good oral hygiene and maintaining a normal oral hygiene regime throughout transplant.

Receiving preventative advice and the need to avoid or treat potential sources of infection, of which the oral environment is a potential source, were the two main reasons highlighted by this cohort for attending the dental assessment appointment.

Participants saw good oral hygiene as a way of combating oral ulceration and mucositis following HSCT, in keeping with the evidence which suggests improvements in oral hygiene and periodontal health can reduce the severity and duration of mucositis (Da Silva Santos et al., 2011, Kashiwazaki et al., 2012, Gürgan et al., 2013).

The individuals in this cohort discussed the difficulties in maintaining their normal oral hygiene regime whilst in hospital during the transplant period. They highlighted that their priorities changed, in particular, if admitted to intensive care or due to fatigue or illness. Additionally, experiencing mucositis, and the associated pain or bleeding from the oral cavity, reduced

the frequency of toothbrushing. Hence other techniques such as mouthwashes were advised to cleanse the oral cavity.

The individuals within this study felt that an increased awareness of oral hygiene on the ward, such as posters and personalised preventative plans, would have been a useful aid to remind them to brush their teeth or use mouthwash.

4.6.1.2 Patient experience of the care received

The individuals who were interviewed within this study were grateful to be seen within a specialist dental setting either because of the enhanced knowledge and understanding that the dental specialists or specialty trainees had about their cancer diagnosis and treatment or because all of the patients are referred to one place and so everyone was presumed to be receiving the same standard of care. It was felt that having a single dental unit would improve the communication with the Haem-oncology team as opposed to patients seeing multiple general dental practitioners.

The study highlighted that further information was required for patients receiving HSCT regarding the types of dental treatment available together with the different treatment modality options. The treatment plan was often dictated by the time available prior to transplant, with the priority being treatment of teeth of poor prognosis and associated signs of infection. Although conscious sedation was a possible treatment modality for the majority of patients, its availability is more limited than treatment with local anaesthetic. One individual within this study highlighted his dental anxieties and preference for sedation, unfortunately his treatment was not provided

due to the limited time prior to transplant and cancelled appointments, however, following his HSCT, he felt more confident in managing treatment with local anaesthetic alone.

Many studies within the literature highlight time limitations prior to transplant as a particular challenge in treating this cohort of patients, in addition to their medical status, including thrombocytopenia and neutropenia, impacting on the ability to arrange suitable appointments to complete the necessary dental treatment (Elad et al., 2003, Yamagata et al., 2006, Bosden Braber et al., 2015, Bogusławska-Kapała et al., 2017, Mendes et al., 2018).

Additionally, individuals within this study highlighted the difficulties and challenges in attending further appointments for dental treatment due to the pressures of attending haem-oncology review appointments, treatment appointments for chemotherapy and radiotherapy, additional medical appointments and being a hospital inpatient within the hospital for prolonged periods of time. These conflicting demands on a patients' time further limited the time available to provide the necessary dental treatment and so perhaps, closer liaison with the medical team or earlier referral would relieve some of this time pressure.

This cohort had mixed views regarding future dental care provision following HSCT, with some individuals seeing themselves as "transplant patients" and so presumed that care would be continued in a specialist setting whereas others would prefer to see their own dentist due to the rapport that they have with them, the normalisation of seeing a dentist in

community, and care being available closer to home. The literature highlighted that, while patients preferred to be seen by their own GDPs, they also wanted reassurance of treatment in a specialist centre. Reasons given by the patients in 2 studies for specialist dental care included refusal of GDPs to treat them due to their medical status and a lack of patient trust in their own GDP to be able to provide treatment outside of a hospital setting (Nuernberg et al., 2016, Mendes et al., 2018). A further study suggested a shared care approach to providing dental treatment for this patient cohort, with more invasive treatment being provided within the hospital but with simple treatment provision at a dental practice closer to the patient's home, thus reducing the impact on their daily routine (Elad et al., 2003).

To ensure effective shared dental care for this patient cohort, education of specialist dental staff, general dental practitioners and the patients' medical team is required to ensure that everyone is aware of the suitability of the dental treatment and the appropriate safe haematological reference ranges for each setting.

This present study suggests there were difficulties in arranging a follow up appointment post-HSCT. Some of the individuals interviewed had outstanding dental treatment and were delayed in being re-referred to the Special Care Dentistry Department following their transplant. This again highlights the need for more effective communication with both the medical and dental team and an update to the current care pathway with patient specific information regarding follow up appointments, which may be useful in improving access to care post-transplant. If the patient was well and haematologically stable then the review and treatment could take place with

the patient's own GDP. However, national guidance suggests ongoing dental care in a specialist setting for a year following HSCT (The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

In addition, long term complications of HSCT such as xerostomia and GvHD highlight the need for further dental surveillance following transplant since patients with these complications are at increased risk of dental caries and/or of malignant change with oral GvHD. The literature suggests the dental reviews would be appropriate within the primary care setting (Petti et al., 2013, Torres-Pereira et al., 2014, Santos-Silva et al., 2015, Tsushima et al., 2015, Weng et al., 2017).

4.6.1.3 Consequence of medical management

There are numerous complications following HSCT that can affect patients in the early or late stages following transplant.

Infections are a severe risk following HSCT due to the immunosuppressive nature of patients during the immediate post-transplant period. Within this cohort, participants described the variety of infections that they had experienced and the side-effects of the drugs used to treat them. Many of the individuals experienced multiple admissions to hospital following chemotherapy or HSCT for infections of a bacterial and viral nature including pneumonia. In addition, they described fungal infections of the mouth and other organs including the lungs.

The immunosuppressed nature of individuals during transplant is the rationale for a pre-HSCT dental assessment and treatment of any dental pathology (Epstein et al., 2009, The Royal College of Surgeons England /

British Society of Disability and Oral Health, 2018). There is limited evidence to support this with some studies finding no difference in odontogenic infections in patients who have received dental treatment compared to those that have not (Melkos et al., 2003, Yamagata et al., 2006, Yamagata et al., 2011, Barrach et al., 2015). In contrast, other studies describe odontogenic infections causing septicaemia or organisms present in the oral cavity being identified as the likely cause of sepsis (Akintoye et al., 2002, Soga et al., 2008, Masaya et al., 2013), with one study highlighting two cases of sepsis as a consequence of oral mucositis (Yamagata et al., 2011). All of these studies describe sepsis as a consequence of HSCT and therefore the management of dental pathology and improvement in oral hygiene would theoretically lower the risk of sepsis associated with the oral cavity.

Graft versus Host disease (GvHD) is a well-documented acute and chronic complication of allogeneic HSCT affecting between 30-60% of HSCT survivors (Filipovich et al., 2005). Individuals within this study highlighted the varying nature of GvHD presentation and severity, from some describing a skin rash and changes in appearance to their oral cavity to others describing a severe impact of GvHD of the gut causing malnutrition and need for prolonged hospital stays.

GvHD impacts significantly on overall mortality. Within the literature, GvHD is the cause of death in 32% to 70% of cases. However, the studies are over a 10 year and 5 year period respectively (Mays et al., 2013, Duncan et al., 2015).

In addition, for patients surviving with chronic GvHD, there is an impact on their quality of life. One study compared the quality of life of those who had both extra-oral and oral presentation of GvHD to that of those who had extra-oral or oral presentations alone. They found no meaningful difference between the groups, however the authors found that the disease severity was worse in the groups where there was extra-oral presentation of the disease (DePalo et al., 2015).

Oral complications were experienced by the individuals within this study, they described having a sore mouth (mucositis) with associated difficulties in toothbrushing, changes in tastes (dyguesia) and experience of candida infections. However, as a cohort they were able to contextualise these complications in regard to the rest of their transplant. Disturbances in taste was discussed at length by multiple individuals within this study and although self-limiting, caused a lasting impression on these participants during their transplant period.

One study within the literature highlighted that altered taste was more prevalent in patients who receive total body irradiation as part of their allogeneic HSCT (Brand et al., 2009).

A common oral complication which was not described by this cohort was that of xerostomia. Xerostomia is again a self-limiting complication of HSCT and has been found in the literature to improve within 1 year following HSCT (Laaksonen et al., 2011, Mauramo et al., 2017). However, the dental consequence of hyposalivation is that of dental caries and again warrants dental review and necessary intervention, in particular prevention advice

following HSCT (Castellarin et al., 2012, Ertas et al., 2014, The Royal College of Surgeons England / British Society of Disability and Oral Health, 2018).

Oral complications can impact on difficulties in eating and the evidence suggests that good nutrition during HSCT can improve recovery and reduce length of hospital stay (Espinoza et al., 2016, European Society for Blood and Bone Marrow Transplantation, 2019e). The individuals within this study highlighted difficulties in eating either as a consequence of a sore mouth, change in taste, or a reduced appetite due to the emotional impact of transplant. To combat these difficulties adjuncts to feeding were implemented, such as supplemental nutrition or nasogastric tubes and in some cases total parenteral nutrition was required. Within this cohort, some participants accepted any additional nutrition that was suggested as a way of recovering quicker and reducing the inpatient stay, whereas others highlighted their reluctance to have a nasogastric tube as they saw it as uncomfortable and distressing.

Individuals within this study also highlighted the other effects of their treatment, particularly the overall impact on their life. They described changes in their appearance, particularly the impact of hair loss, needing to use an electric razor due to the risk of bleeding and also the amount of time spent in hospital with one participant spending their 21st birthday as an inpatient. They also described continued anxiety regarding infection risk and also the guilt associated with surviving.

4.6.1.4 Psychological impact of treatment

The diagnosis of a haematological malignancy and its treatment (chemotherapy, HSCT) present a challenging and life-threatening period for a patient with subsequent psychological impact.

Individuals within this cohort described the anxiety experienced in regard to the period prior to transplant but also the continued anxiety following transplant with regard to their longer term survival. Before transplant, individuals described periods of relapse and time spent on the donor waiting list awaiting a match. In addition following transplant, patients described the effect of their experience on their daily life, such as continued awareness of infection. The biggest worry for participants was the fear of relapse of the disease and the need for further medical intervention. One participant highlighted his feelings that he wouldn't be able to go through the HSCT process again.

Within the literature, disease relapse, concerns regarding medical status, and appearance are prevalent as post-HSCT trepidations (Mosher et al., 2011). In addition, the effect on family life and employment status feature highly (Mosher et al., 2011). One study found that those who find employment with higher incomes have a better functional status and have a better quality of life following transplant (Mosher et al., 2011). Other studies have found that an optimistic attitude towards the future together with a good social support network were related to a better ability to cope post-transplant (Beeken et al., 2011, Rueda-Lara and Lopez-Patton, 2014). In addition mental health issues, such as depression, post-traumatic stress disorder and

delirium feature highly with patients following HSCT (Rueda-Lara and Lopez-Patton, 2014).

Within the Stem Cell Transplantation and Cellular Therapy Unit (CCC), counsellors were available to help patients through the process of HSCT. This service, although limited, was also available following HSCT. A specific long term service for these patients may be helpful in negating some of the emotional and mental consequences of this distressing period within a patient's life.

In addition to general anxiety, specific dental anxiety is prevalent within the population. The most recent Adult Dental Health survey in 2009 highlighting that 48% of the adult population have moderate to severe dental anxiety. It is therefore unsurprising that individuals within this patient cohort were anxious of both dental treatment and pre-HSCT dental assessment (National Health Service, 2009). Some of the participants within the cohort who were unable to have their dental treatment prior to transplant felt that having experienced the transplant process, their dental anxieties had been alleviated somewhat and they felt more relaxed about attending dental appointments in the future.

Other participants highlighted anxieties around future dental treatment and the appearance of their teeth and were unsure who would provide the necessary dental treatment in the long term. This again highlights the need to improve delivery of information to patients on the service that is provided as part of their care pathway.

4.6.1.5 Quality of Life

The second element of this study was to review the participants' quality of life in reference to their bone marrow transplant, oral health and experience of GvHD through three separate quality of life questionnaires (see Methodology section 14.4 for full description of each questionnaire).

On reflection, the use of these questionnaires as a part of this study was not fit for purpose as they were only used at one point in time and therefore did not allow pre-/post- HSCT comparisons. Thus, they provided information of limited value within the current study.

Overall, the quality of life of these 7 individuals was good in terms of their post-BMT experience, experience of GvHD and oral health. However, there were elements of each questionnaire that showed where quality of life was deemed lower.

4.6.1.5.1 OHIP-14

From an oral health perspective some participants highlighted concerns with the appearance of their teeth and feelings of embarrassment in relation to their teeth. This links with the qualitative results where participants highlighted concerns related to dental follow up, anxieties around missing teeth subsequent to extractions, and also a concern regarding staining of their teeth following medical treatment, including prolonged use of chlorhexidine mouth wash.

There has been limited use of oral health related quality of life (OHRQoL) questionnaires for haematopoietic stem cell transplant recipients. However, one study conducted in Brazil in 2015 compared OHIP-14 of

patients prior to HSCT to a group of healthy individuals. Although there was a weak correlation of oral health related quality of life between the groups, they found that patients awaiting HSCT with a severely neglected dentition reported poorer oral health related quality of life. However, their study did not compare results post-HSCT and therefore the impact of the HSCT process on OHRQoL was unknown (Tinoco-Araujo et al., 2015).

The OHIP-14 questionnaire has also been used in two studies evaluating the use of low-level laser therapy (LLLT) in the treatment of mucositis for HSCT recipients. One study found that the use of LLLT had no impact on quality of life between those receiving LLLT and those who did not (Silva et al., 2015). The other study found the QoL for those treated with LLLT improved with time; however as mucositis resolves within 14-21 days the QoL would be expected to improve with time without interventive treatment (Bezinelli et al., 2016).

4.6.1.6 FACT BMT

The FACT-BMT quality of life questionnaire has been designed specifically for patients undergoing bone marrow transplantation, and is usually used prior to and following HSCT (FACTIT, 2010).

Given the limited sample size within the current study, it was difficult to draw conclusions from these results. In general, participants reported having a higher quality of life with regards to their bone marrow transplant particularly with regard to their emotional and social well-being. In addition, participants only completed the questionnaire following their transplant and so comparisons could not be made to their quality of life prior to HSCT.

4.6.1.7 Lee GvHD symptom score

The Lee GvHD symptom score reviews the impact of the multi-organ effect of GvHD on patients' quality of life (Lee et al., 2002, Merkel et al., 2016). The use of this questionnaire has been recommended since 2005 by the NIH to capture the GvHD symptoms and their effects (Merkel et al., 2016).

From the questionnaire the participants within this current study reported a positive outlook on their quality of life in regards to chronic GvHD. The areas where they reported poor quality of life were around the amount of energy they had and also their mental and emotional wellbeing.

As the questionnaire was only completed at one point in time, the time of transplant was different for each individual, it was not possible to compare the results. Participants were asked to consider the questionnaire with regard to the last month, and therefore, as they had their transplant at various times, the symptoms would have been different for each individual. Some may have been on long-term treatment for GvHD (although this was not investigated as part of the study) and they may have adapted and learned to cope with and manage their GvHD symptoms reducing the impact on quality of life.

Within the literature, the Lee GvHD symptom score is ideally used in combination with other quality of life questionnaires. Lee recommends the use of the questionnaire along with the FACT-BMT quality of life questionnaire and the Short Form health survey (SF-36) to ensure a full robust assessment of a patients' quality of life (Lee et al., 2002). Although the current study also used the FACT-BMT questionnaire, the results overall

were limited as the participants were at different stages post-transplant and only completed the questionnaire at a single point in time.

The impact of GvHD on quality of life has been assessed with other quality of life questionnaires. Depalo et al. utilised the SF-36 and FACT-BMT to assess if there was any differences in quality of life when comparing extra-oral GvHD, oral GvHD and those experiencing both. They found that quality of life was lower, if there was an extra-oral component of the disease (DePalo et al., 2015).

The Lee GvHD symptom score is a validated specific questionnaire that would give valuable results if utilised correctly within the framework of a potential future prospective study (Lee et al., 2002, Merkel et al., 2016).

4.6.2 Limitations of the study

There were a number of limitations of this study. Firstly the sample size was small with only 7 participants being interviewed. The length of the interviews ranged from 15 minutes to 45 minutes which could be a reflection of the limited experience of qualitative research of CW-D or reflective of the fact that some participants felt more comfortable to discuss their experiences in depth, whereas others were more withdrawn. In addition, although no new themes appeared to be emerging, achievement of data saturation is unclear due to the difficulties discussed previously in Section 4.4.9 and Section 4.5.3. Unfortunately it was not possible within the time constraints of the study to conduct further interviews.

On reflection only a select number of patients have an allogeneic HSCT within the Clatterbridge Cancer Centre each year, hence the variety of

individuals was broad, with HSCT being the recommended treatment for multiple diseases, and these diseases affecting patients of any age and both genders. There is therefore the possibility that saturation could never be reached. Furthermore, the topic guide for this study was again rather broad, looking at both the pre-HSCT assessment and dental treatment but also the post-HSCT complications and the journey as a whole. This gave a broad variety of responses and perhaps, for future research a more niche topic guide would be required to increase the quality of the responses.

A further challenge of this study was the recruitment process. As mentioned throughout the study the participants had multiple conflicting demands on their time, with their appointments being flexible in regard to timings. This made it difficult to arrange a suitable time for participants to attend for interview. Participants were also reluctant to attend the hospital on a different day to their appointments, therefore for future studies, a neutral environment away from the hospital and closer to the patients' home may be preferable but would take away the availability of the medical team should any issues arise.

Additionally, the recruitment process only captured the views of participants who wished to be engaged with medical research. There were patients who were approached who declined to take part in the research project, one of whom was not happy that he had not had a denture constructed as part of his dental treatment. His views of the service would have been extremely valuable in this study. For future studies the use of a gate-keeper, e.g. a specialist research nurse, to recruit participants and facilitate initial rapport with the research may increase recruitment rates.

The next limitation of this study was the fact that given the small number of patients available for recruitment, the time since the patients' transplant was varied, with some having their transplant in the last year, to others having had their transplant a number of years ago. This raised the issue of recall bias and whether what they are reporting was accurate (Green and Thorogood, 2014b). For future studies it would be preferable to interview participants within a defined timespan following transplant to ensure more accurate information and perhaps information that was more in depth and valuable.

As mentioned previously this was CW-D's initial experience of qualitative research and so, with experience and guidance, the interview and analysis techniques would be improved upon.

Unfortunately, the use of the quality of life questionnaires within this project added limited additional value to the study. The sample size was small and all of the participants were at a different stage post-HSCT and given the difficulties in recruitment it was not possible for this to be standardised. In addition, the questionnaires only captured one point in time and there were no results to which to compare them to. In future, prospective studies could be devised to address the need for standardisation of the timing of the questionnaire for each individual. In addition, completion of the questionnaire at different stages of the transplant process and recovery would be necessary to evaluate changes in quality of life and may increase the validity of the results.

4.6.3 Reflexivity

Reflexivity is a necessary part of qualitative research whereby the impact of the researcher on the interview, analysis and reporting process is explored. Ideally within qualitative research the researcher is invisible, however this is unlikely to be possible in most projects (Green and Thorogood, 2014a, Ritchie et al., 2014c).

There were multiple potential areas of bias with regards to reflexivity in this study. The researcher, CW-D, worked as a Speciality Registrar within the Special Care Dentistry Department and participants were made aware of this at the time of the study. The knowledge that the person conducting the interview was a dentist is likely to have had an effect on the participants' responses. Also the researcher herself had preconceived knowledge and experience of treating this patient cohort which may have influenced not only the interview process but the analysis.

In addition, it was difficult for CW-D to detach from the emotive side of the participants' experiences and not to provide reassurance throughout the interview. Becoming a researcher as opposed to a clinician was a difficult achievement, but became easier with the later interviews.

As the interviews were emotive in their content, and in some cases distressing, the process of transcribing all of the interviews provided an effective method of debrief for CW-D. In addition, discussion around the main themes of each interview with clinical colleagues, along with supervisors, helped gain perspective on the research project.

For future studies the use of a gate keeper in recruiting patients and forming the initial introduction between the potential participant and the researcher may improve recruitment. Additionally, if the researcher was someone non-specific to the patients' medical or dental team, then the participant responses may be more open.

4.6.4 Strengths of the study

There were also a number of strengths of this study. Conducting qualitative research allowed for an in-depth perspective directly from the patients using this service.

The study did not look solely at the dental service and oral health perspective but also the medical management and therefore improvements to both services could be implemented in the future to provide a positive impact on patient care.

In order to make the study more reliable, supervisors reviewed some of the transcripts and all of the themes and results were reviewed by ST and RH.

Importantly, conducting this qualitative research has highlighted that it is possible to recruit from this hard to reach and vulnerable patient cohort. However, for future research a more specific patient population and topic guide would be required.

Although the quality of life questionnaires did not add value to this project, they were all validated questionnaires and so if used correctly and in combination would be able to show changes in quality of life in regard to the experience of bone marrow transplant, effects of GvHD and oral health.

4.6.5 Application to clinical practice

With the views of the individuals within this study in mind, a number of improvements to the service could be implemented.

Participants highlighted the need for more information on the reasons for a dental assessment and follow up dental care. There was the suggestion made for personalised prevention plans and reminders to be placed on wards with regards to oral hygiene. It would be possible to produce posters or infographics to provide oral hygiene information and prompts, individual preventive plans to be given to each patient at assessment. The production of information leaflets to describe the care pathway, what to expect, the dental care received and also the importance of follow up dental care would also help to meet the patient information need.

The care pathway requires modification as many participants highlighted the delay in attending for dental treatment following HSCT. Education for the dental team in the Special Care Dentistry Department, the patients' medical team and also General Dental Practitioners is necessary to ensure that the patient is being referred to the correct service at the right time. A shared care approach would be ideal, allowing patients to have simple and aesthetic treatment closer to home with their own GDP and more interventive dental care provided in the secondary care setting, again dependant on the severity and stability of the individuals' haematological status.

A further application to practice involves the psychological aspect of the HSCT process, as many participants in this study highlighted prior or

current anxieties with regards to their medical status. The current counselling service available for HSCT patients it is limited however, an increased availability throughout the transplant process would be helpful to better support patients' psychological needs. In addition, one participant in this study highlighted that patient advocates would be helpful in order to describe the transplant journey and provide reassurance as they are the ones who have experienced it first-hand.

4.6.6 Future research

Future research of both a qualitative and quantitative nature is required for this patient cohort in order to evaluate the impact of dental treatment on patients undergoing HSCT. Overall the participants within this study found that having a dental assessment prior to transplant was useful and reassuring. However, the sample size of the study was small and it is unclear if saturation was reached.

A mixed methods approach involving a prospective longitudinal study would allow for dental and medical data collection and semi-structured interviews regarding pre-HSCT dental care to be completed at the time of dental assessment and then at 100 days post-HSCT to explore patient views on dental treatment and oral complications. Limiting recruitment to a specific disease process, e.g. AML or myeloma, may aid in achieving saturation, as the participants may have more in common such as their chemotherapy regimens, ages and gender.

A study using the quality of life questionnaires OHIP-14, FACT-BMT and the Lee GvHD symptom score would be valuable to assess the changes

in quality of life and experience of GvHD for these individuals (Slade, 1997, Lee et al., 2002, FACTIT, 2010). The questionnaires would need to be completed prior to transplant and then at standardised intervals following transplant to allow comparisons to be made.

4.6.7 Conclusion

Completion of this study provided insight into a patient's views of dental treatment and oral health within the context of their transplant journey.

From the interviews completed, four key themes materialised allowing exploration of the impact of dental treatment prior to and directly following HSCT and also participants' future concerns with regards to oral health.

Overall, participants had an understanding of the importance of a pre-HSCT dental assessment regarding increased risk of infections during their period of immunosuppression with the oral environment providing a potential source of infection. The majority felt reassured by having their dental treatment completed in a specialist setting as they felt the clinicians had an increased understanding of their medical conditions.

Participants had insight into the importance of maintaining good oral hygiene throughout transplant. However, they also alluded to the change in priorities with regards to daily routines due to the resulting fatigue and malaise of the transplant process and the reduction in the ability of participants to complete normal oral hygiene practices.

There was confusion regarding ongoing dental care and the dental treatment available to them following transplant.

The quality of life questionnaires had limited value within this study, however, it was positive that each of the seven participants reported a good level of quality of life.

Future work is required on the quality of life of this HSCT patient group particularly with reference to oral health. To aid in establishing the impact of

dental treatment on HSCT, the use of a mixed methods design would be useful in providing a rich data set.

To conclude, completion of this study will enable changes to the current care pathway for patients including provision of more written information as to the reason for dental assessment, importance of continued oral hygiene and follow up dental care post-HSCT. It also provides a base for future research to build upon with regards to improving the oral health care for this patient group.

5 Chapter 5: Overall conclusion

In conclusion, the results of this study are consistent with the available literature and this study provides an initial insight and overview to the effects of dental treatment on patients' outcomes following allogeneic HSCT.

From the first project it can be seen that for this cohort of patients, there were no detrimental effects of dental treatment following transplant, with no patients experiencing neutropenic sepsis as a result of an odontogenic infection. In addition, the vast majority of patients received prevention advice that impacts on oral complications following transplant. Within the cohort there was evidence of patients experiencing oral complications including mucositis, xerostomia and stomatitis, highlighting the need for prevention advice but also ongoing dental surveillance following transplant.

From the second project, the qualitative views of participants highlighted their appreciation of the dental review prior to transplant and reassurance in seeing a specialist dental unit team who were knowledgeable of their medical condition and could communicate easily with the medical professionals involved in their care. However, participants also highlighted their confusion, post-transplant, as to how their continuing dental care would be managed. Further efforts to inform and educate both medical and dental professionals regarding the dental management of post-HSCT patients would be beneficial to patients.

Further specific research is required as to the impact of oral health and HSCT on a patient's quality of life which was not possible within the time limitations of this study. In addition, further prospective longitudinal research

is required to determine the clinical effects and outcomes of dental treatment on HSCT recipients. Future studies would need to involve multiple centres to ensure that a sufficient cohort of patients is recruited. The use of the directed acyclic graph within future research would allow for minimal adjustments of the variables within the statistical analysis.

From a service perspective positive improvements can be made to the established care pathway as a result of this research. Improving the communication with both the medical team and patients with regards to the initial referral and treatment could ensure a more predictable completion of dental treatment prior to transplant. The production of information leaflets is required for patients to improve their knowledge of the service, act as prompts during the transplant period, and to clarify the re-referral post-transplant. From a medical perspective standardising the record keeping for both mucositis and GvHD would allow for consistent recording and provision of the most appropriate management of these oral complications.

Introduction, embedment and review of these improvements to the service would hopefully prove helpful for patients at a particularly challenging and vulnerable stage in their lives.

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7 Appendices

7.1 Appendix 1: HRA approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Amit Patel
Division of Stem Cell Transplantation and Haemato-Oncology
Clatterbridge Cancer Centre Liverpool, Royal Liverpool University Hospital, Floor 2 Duncan Building
Prescot Road, Liverpool
L7 8XP

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

17 April 2018

Dear Dr Patel

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The influence of dental assessment prior to allogenic stem cell transplantation on patient centred outcomes including graft versus host disease and quality of life.**
IRAS project ID:	**224849**
Protocol number:	**914**
REC reference:	**18/NW/0043**
Sponsor	**The Clatterbridge Cancer Centre NHS Foundation Trust**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales*, as well as any documentation that has been updated as a result of the assessment.

*'In flight studies' which have already started an SSI (Site Specific Information) application for NHS organisations in Wales will continue to use this route. Until 10 June 2018, applications on either documentation will be accepted in Wales, but after this date all local information packs should be shared with NHS organisations in Wales using the Statement of Activities/Schedule of Events for non-commercial studies and template agreement/ Industry costing template for commercial studies.

This is a single site study sponsored by the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA/HCRW Approval.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA/HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA/HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Dr Maria Maguire
Tel: 0151 556 5321
Email: maria.maguire2@nhs.net

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **224849**. Please quote this on all correspondence.

Yours sincerely

Kevin Ahmed
Assessor

Telephone: 0207 104 8171
Email: hra.approval@nhs.net

Copy to: *Dr Maria Maguire, Sponsor Contact, The Clatterbridge Cancer Centre NHS Foundation Trust*

List of Documents

The final document set assessed and approved by HRA/HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper		19 March 2018
Interview schedules or topic guides for participants [Appendix 15 example topic guide]	1	29 October 2017
IRAS Application Form [IRAS_Form_02012018]		02 January 2018
Other [Appendix 8 final data collection form]	2	22 March 2018
Other [thank you letter]	1	29 October 2017
Other [Girvan Burnside CV]		25 July 2017
Other [Response to Validation]		19 January 2018
Other [Charlotte Wilson Dewhurst CV]	1	11 December 2017
Other [Dr K Taylor CV]		
Other [Appendix 1 glossary]	1	29 October 2017
Other [Appendix 2 care pathway]	1	29 October 2017
Other [Appendix 3 key search terms]	1	29 October 2017
Other [Appendix 4 literature summary]	1	29 October 2017
Other [Appendix 5 SIGN levels of evidence]	1	29 October 2017
Other [Appendix 6 quantitative study groups]	1	29 October 2017
Other [Appendix 9 analysis flowchart]	1	29 October 2017
Other [Appendix 10 sample framework]	1	29 October 2017
Other [Appendix 11 recruitment eligibility]	1	29 October 2017
Other [Appendix 16 budge]	1	29 October 2017
Participant consent form [Appendix 13 consent form]	4	22 January 2018
Participant information sheet (PIS) [Appendix 12 participant information sheet]	4	11 December 2017
Research protocol or project proposal [Protocol]	1	29 October 2017
Summary CV for Chief Investigator (CI) [Dr Amit Patel CV]		01 October 2017
Summary CV for student [Charlotte Wilson-Dewhurst CV]		15 November 2017
Summary CV for supervisor (student research) [Shelagh Thompson CV]		15 November 2017
Validated questionnaire [Oral Health Impact Profile (OHIP-14/ Slade 1997)]		
Validated questionnaire [Oral Health Impact Profile OHIP-14 Slade 1997]		
Validated questionnaire [FACT-BMT_ENG_Final_Ver4]		18 December 2013

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA/HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a non-commercial single site study taking place in the NHS where that single NHS organisation is also the study sponsor. Therefore no study agreements are required.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	No application for external funding has been made.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments

Section	Assessment Criteria	Compliant with Standards	Comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator should be appointed at study sites GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
As a non-commercial undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable, except where local network staff employed by another Trust (or University) are involved (and then it is likely that arrangements are already in place). Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in A18 of the IRAS form would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

7.2 Appendix 2: Sponsorship approval letter

NHS
The Clatterbridge Cancer Centre
NHS Foundation Trust

Clatterbridge Road
Bebington
Wirral
CH63 4JY

Tel: 0151 556 5000
Web: www.clatterbridgecc.nhs.uk

Our Ref: MM\C0938\JK

14th May 2018

Charlotte Wilson-Dewhurst
SCD ACF/StR
Liverpool University Dental Hospital
Pembroke Place
Liverpool
L3 5PS

Dear Charlotte

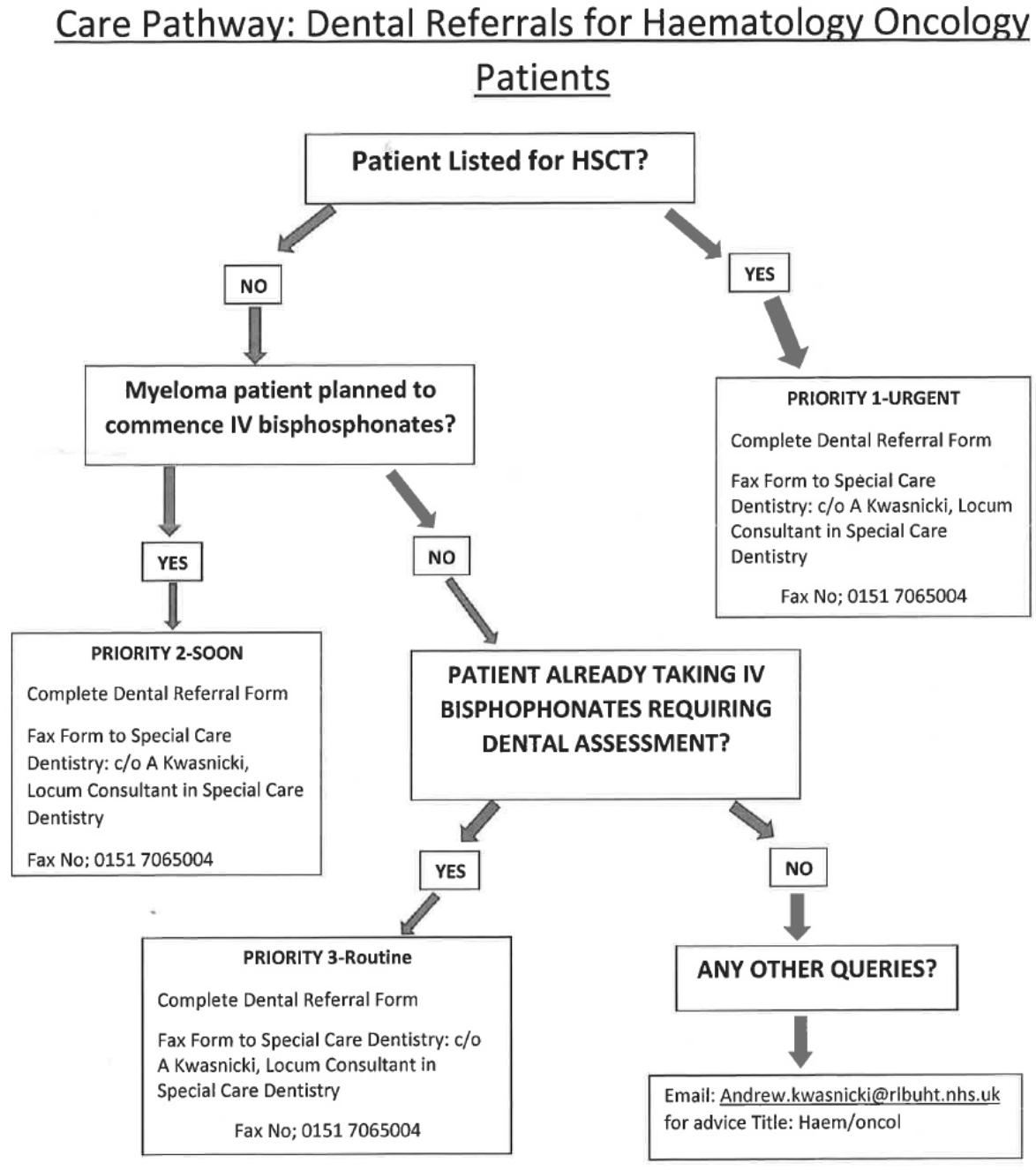
SHORT STUDY TITLE:	**Effect of dental interventions on allogenic HSCT outcomes**		
FULL TITLE:	**The influence of dental assessment prior to allogenic stem cell transplantation on patient centred outcomes including graft versus host disease and quality of life.**		
R&DD REF:	**C0938**	**IRAS ID:**	**224849**
NRES REF:	**18/NW/0043**	**EUDRACT NO:**	**Not applicable**
PROTOCOL & APPENDICES :		**Version: 6**	**Date: 29-10-2017**
PARTICIPANT INFORMATION SHEET:		**Version: 4**	**Date: 11-12-2017**
PARTICIPANT CONSENT FORM:		**Version: 4**	**Date: 22-01-2018**

As Sponsor, I confirm that following receipt of all regulatory approvals and study documents, The Clatterbridge Cancer Centre NHS Foundation Trust gives approval for the above study to be conducted on Trust premises, in line with the Health Research Authority (HRA) guidelines on Assess, Arrange and Confirm. This acceptance is in accordance with UK Policy Framework for Health and Social Care Research.

Yours sincerely

Dr Maria Maguire
Research Manager

7.3 Appendix 3: Care pathway



** For urgent or soon appointments expect an email response within 1 week, if no response please email patient details to Andrew.kwasnicki@rlbuht.nhs.uk , Beryl.Learman@rlbuht.nhs.uk and Christina.vilabea@rlbuht.nhs.uk

7.4 Appendix 4: Key search terms

Search Number	Key terms (MEDLINE, Scopus, EBSCO, PsycInfo)
1	haematopoietic stem cell transplant AND dental treatment
2	haematopoietic stem cell transplant OR bone marrow transplant AND dental care OR comprehensive dental care OR dental treatment
3	haematopoietic stem cell transplant AND dental treatment AND “quality of life”
4	haematopoietic stem cell transplant OR bone marrow transplant AND dental care OR comprehensive dental care OR dental treatment AND “quality of life”
5	haematopoietic stem cell transplant OR bone marrow transplant AND osteonecrosis OR bisphosphonate associated osteonecrosis of the jaws
6	haematopoietic stem cell transplant AND dental treatment AND “graft vs host disease”
7	haematopoietic stem cell transplant AND dental treatment AND mucositis
8	haematopoietic stem cell transplant AND dental treatment AND xerostomia OR “dry mouth”
9	haematopoietic stem cell transplant AND dental treatment AND “neutropenic sepsis”
10	haematopoietic stem cell transplant AND dental treatment AND mortality

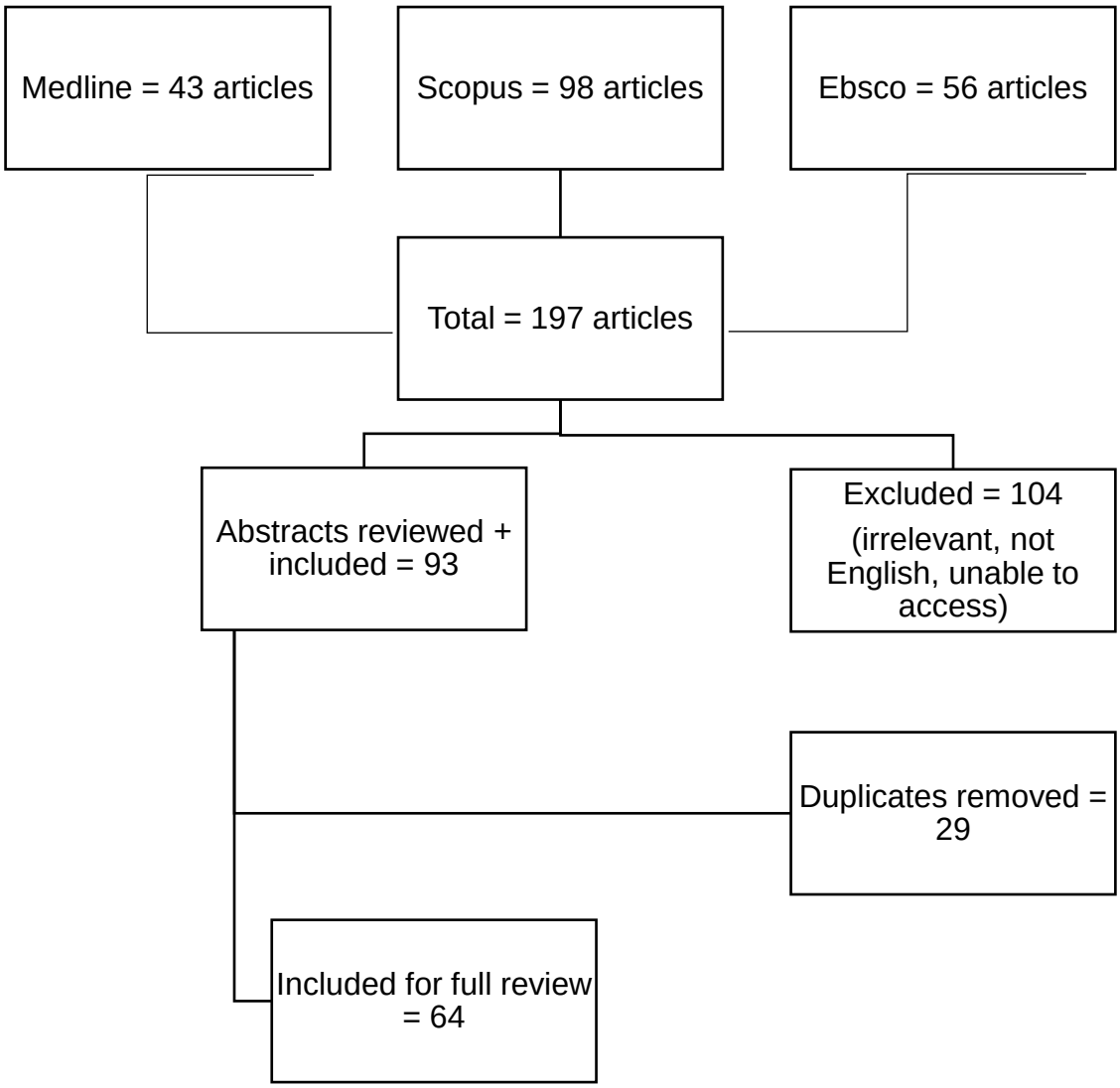
7.5 Appendix 5: Example search strategy

Search terms:

HSCT OR haematopoietic stem cell transplant OR transplant conditioning

AND

Comprehensive dental care OR dental care OR oral health



7.6 Appendix 6: Literature summary

Dental Assessment

Author/ Title /**Level of Evidence**	Sample Characteristics	Study Design	Summary of Findings
(Abed et al. 2019) Oral and dental management for people with lymphoma **4**	No sample described – review article/expert opinion	Review article/expert opinion No structured literature review described	Describes treatment for lymphoma including HSCT. Describes pre HSCT dental assessment, haematological values and post-HSCT review Describes GvHD as a complication of allogeneic HSCT.
(Boguslawska-Kapala. A. et al. 2017) Oral health of adult patients undergoing hematopoietic cell transplantation. Pre-transplant assessment and care **4**	No sample described – review article	Review article/expert opinion No structured literature review described Described development of their local protocol for treatment pre-HSCT	Gives a well-balanced argument for the provision of dental care prior to HSCT – discussed radical vs minimalistic treatment plans Discusses limitations in providing treatment – medical status, timing of appointments Highlights risk of providing treatment pre-HSCT – thrombocytopenia, neutropenia Discusses importance of providing oral hygiene due to post-transplant complications – xerostomia, mucositis.

(Burke et al. 2014) Dental management during stem cell transplantation **4**	No sample described – review article	Review article/expert opinion No structured literature review described.	Describes stages of HSCT – harvest, conditioning, infusion Describes complications of chemotherapy Describes post-HSCT complications – graft rejection, GVHD Describes the role of the dentist and the dental team. Describes the importance of timing dental treatment
(Durey. K. et al. 2009) Dental assessment prior to stem cell transplant: treatment need and barriers to care **3**	94/116 complete dental records for patients undergoing HSCT were reviewed M:F = 52:42 Average age:49years (18 – 67years) Transplant type: unknown	Subject dental records were reviewed data on subject demographics, presenting conditions and dental treatments along with any complications were collected	Referral for subject was on average 31.5days prior to HSCT, subjects were seen on average within 8days of referral. 79.5% had periodontal disease but often unable to perform BPE due to lack of information about haematological values. 93.6% of subjects had oral disease 94.7% of subjects required dental treatment – 74.5% active treatment and 20.2% OHI alone. Those subjects who were regular dental attenders (29.8%) required fewer extractions

(De Paula Eduardo. F. et al. 2011) Oral care in Brazilian bone marrow transplant centres **3**	12/36 bone marrow transplant centres responded to the questionnaire These centres account for 47% of BMT completed in Brazil	Questionnaire involving open and closed questions was sent to 36 BMT centres in Brazil. Questionnaire looked at who was part of the MDT, if dental assessment and treatment is provided prior to BMT, if delays have been caused to BMT due to oral conditions, use of an oral care protocol, use of sodium bicarbonate mouthwash, use of laser therapy for mucositis, use of antibiotic cover and protocols for GVHD.	33.3% response rate 100% of centres had a dentist as part of the MDT 100% of centres provided an oral health assessment prior to BMT 75% reported delaying BMT due to dental pathology 41.7% of centres thought OHI was the most important recommendation 41.7% of centres recommended the use of sodium bicarbonate mouthwash, with 75% recommending chlorhexidine mouth rinse. 75% of centres used laser therapy in the treatment of mucositis either routinely or sporadically 33.3% of centres had a protocol for GVHD but use was variable.
(Elad. S. et al. 2003) Time limitations and the challenge of providing infection-preventing dental care to hematopoietic stem-cell transplantation patients **3**	46/86 consecutive HSCT patient's notes were reviewed. 46 patients examined by hospital staff July 1997 – October 1998 M:F = 25:21 Average age – 37years	Retrospective examination of case notes Patient demographics, planned HSCT, details of dental assessment, details of dental treatment and length of time prior to HSCT were recorded.	Calculus most common dental finding (54.3%) Caries was diagnosed in 50% of cases Dental treatment included scaling and OHI (47.8%), simple restorations (39.1%), dental extractions (19.5%) and were often multiple (10.8%)

			Average time from assessment to HSCT was 20.65 days Complex MH of patient cohort makes scheduling difficult Queried need for involving community dental service in treating these patients.
(Elad. S. et al. 2015) Basic oral care for haematology-oncology stem cell transplant recipients: a position paper paper from the joint task force of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT). **4**	Review paper To develop a protocol to aid practitioners in treating patients with haematological malignancies	Review paper/ expert opinion paper No clear methodology to literature review	Recommends dental treatment pre- and post- HSCT – provides a basis for consensus. Multidisciplinary team approach. Further research is required within this area.

(Epstein. J et al. 2009) Advances in hematologic stem cell transplant: An update for oral health care providers ¾	No sample described – review article	Review article/expert opinion No structured literature review described.	Provision of background information of HSCT in the treatment of malignancies, recent progresses and appropriate advice for oral care providers. Highlights complications affecting the oral cavity; mucositis, infection, bleeding, GVHD, xerostomia, dysgeusia, secondary malignancies. Describes the oral care involvement required at each stage of HSCT.
(Mawardi. H. et al. 2014) Cost analysis of dental services needed prior to hematopoietic cell transplantation **3**	423 subjects M:F= 243:162 Age range: 18-72 January 2005 – June 2007 Subjects had had a dental assessment prior to HSCT	Retrospective study From patients dental records cost of dental treatment were estimated along with the reimbursement by insurance companies.	Caries prevalence = 23% 45.6% of subjects required restorations 20.5% required 1 or more extractions Average cost $275 or $384 dependant on insurer Dental assessment is assumed to reduce overall costs for patients undergoing HSCT, than increased stay in hospital if the patient acquires septicaemia
(Mendes et al. 2018) What haematopoietic stem cell transplant patients think about health and oral care: A qualitative study in a Brazilian health service	17 participants recruited, 16 participants interviewed M:F = 9:7 Age = 46 (26-66 years)	Qualitative study Semi-structured interviews were conducted with a topic guide that was adjusted following the first 5 interviews	Following analysis 3 main themes were highlighted: 1. What is oral health Oral hygiene, diet, aesthetics, lack of pathology 2. Dental treatment as required for haematopoietic transplant

3	Transplant type Autologous: Allogeneic = 4:12 No control group	Topic areas – perceptions on oral health, dental treatment prior to HSCT, Importance of dental treatment prior to HSCT Analysis – content thematic analysis ?single interviewer Interviews conducted on day of dental assessment following transplant Consent completed on the day of transplant	Dental referral at request of medical staff, preference for treatment with own dentist, difficulties in receiving treatment – medical barriers. 3. The importance of dental treatment to perform transplants Reduce infection risk prior to transplant, oral complications post-transplant, success of transplant
(Morimoto. Y. et al. 2004) Dental Management Prior to Hematopoetic Stem Cell Transplant **3**	38 subjects undergoing HSCT 15 subjects for BMT. M:F= 9:6. Average age: 35.9 +/- 11.3 years 23 subjects for PBSCT. M:F 14:9. Average age: 43.3 +/- 15.1 years 1997-2001	Retrospective Review of subjects medical/dental records Recorded background factors, time from dental assessment to HSCT, haematological findings, dental treatments and complications	Patients with platelet counts $<50x10^9$ or $<30x10^9$ safe to provide XLAs and S+P with platelet transfusions. Patients with neutrophil counts 1-$1.5x10^9$ can carry out XLAs and S+P with antibiotic cover. Dental treatment can be problematic due to reduced platelet count and immunosuppression. Need to allow a 2 week healing period prior to transplantation

(Nuernberg. M. et al. 2016) Access to oral care before stem cell transplantation: understand to improve **3**	110 subjects who had a allogeneic stem cell transplant M:F= 69:41 Children: 39 subjects aged 4-11years Adolescents: 23 subjects aged 12-18years Adults: 48subjects >18years March 2014 – March 2015 Non-malignant disease = most frequent conditions	Questionnaire sent to subjects looking at: Patient demographics Diagnosis Access to dental service and history of dental treatment Patients preferences – where they'd like to receive dental treatment Knowledge – oral health prior to HSCT	74% of subjects had received oral care in the previous year. 66% said they did not receive guidance as to oral care prior to HSCT Time limitation is a barrier for accessing dental care for subjects undergoing HSCT 17% of subjects were refused dental treatment by their own dentist due to their medical complexities Subjects would prefer to receive dental treatment at the transplant centre. 29% said they wouldn't trust a dentist to provide treatment outside of a hospital. Use of an outside dental service was statistically associated with income
(Nuernberg. M. et al. 2017) Periodontal status of candidates for allogeneic hematopoietic stem cell transplantation **2-**	62 subjects recruited, 26 excluded due to timing of HSCT therefore 36 included. M:F= 22:14 Age = 25.5 (14-67years) Allogeneic only	Prospective cross-sectional study – survey regarding patients oral health followed by periodontal assessment Single interviewer and examiner – intra and inter-rater reliability calculated. Evaluated visible plaque, bleeding on probing, pocket depths and attachment loss on 6 teeth upper and lower.	There 21/36 participants who had seen a dentist in the last year, with 81% brushing teeth more than 1 x day. 78% of participants denied receiving oral health advice prior to HSCT. Diagnosis of periodontal disease in this cohort was high with 58% having pocket depths >4mm and inflammatory changes.

		Excluded platelet counts <50x10^9 or those who were uncooperative for examination	There was no correlation with bleeding on probing and platelet counts or diagnosis of periodontal disease and neutrophil counts. Highlighted that although patients self reported to have good oral health the majority actually had clinically poor oral health.
(Pelinsari. C.M. et al. 2014) Dental extractions in patients prior to stem cell transplant 3	33 participants M:F = unknown Age = unknown Transplant type = unknown All received at least 1 extraction	Retrospective cohort study Reviewed bleeding complications following extraction on patients prior to HSCT	At the time of extraction 7 patients had platelet levels <100x10^9. Those with platelet counts <50x10^9 received platelet transfusion (2 cases). Fibrillar absorbable sponges were used in 2 patients. No infectious complications despite no antibiotic cover. Extractions prior to HSCT are safe with a recent blood count and assessment of platelet levels.

Dental effect on HSCT outcome

Author/ Title /**Level of Evidence**	Sample Characteristics	Study Design	Summary of Findings
(Akintoye.S. et al. 2002) A Retrospective Investigation of advanced periodontal disease as a risk factor for septicaemia in haematopoetic stem cell and bone marrow transplant **2-**	77/141 patients who received HSCT fulfilled inclusion criteria January 1996 – September 1999 M:F = unknown Average age: 37.3 +/- 11.9years	2 groups - <20% periodontal bone loss and >20% periodontal bone loss Retrospective review of medical and dental notes Dental examination 1-3weeks before transplant and dental treatment Periodontal diagnoses were drawn from radiographs using Schei ruler due to difficulties in recording periodontal probing depth due to lack of haematological values. Blood cultures were drawn if patients exhibited signs of septicaemia	66% of cohort received dental treatment prior to HSCT. 18.2% of sample had >20% horizontal bone loss 72.7% survival rate 63.6% of sample had positive blood culture for septicaemia from which 81 isolates were recovered 20 subjects had blood cultures likely of subgingival/periodontal origin, 23 subjects were positive for microbes from the oral cavity and 49 with organisms from body sites. No statistical significant associations between radiographic bone loss and incidence of septicaemia. Patient cohort are at high risk for infections.
(Bos-den Braber. J. et al. 2015) Oral complaints and dental care of haematopoietic stem cell transplant patients:	160 adults had HSCT 2010 and 2011 101 survived to start of survey 2012 96 responded to survey M:F unknown	Questionnaire to patients included 20 questions asking them to recall the short and long term oral complications following HSCT	8/96 patients had not had a dental assessment prior to HSCT 59% had short term oral complaints the main one being altered taste 28% had long term oral complaints the main one being dry mouth

a qualitative survey of patients and their dentists **3**	Average age: unknown 52/88 dentists responded to their questionnaire	Questionnaire to dentists (following patient permission) asking them to report on dental assessment and treatment for these patients and why it is important No interview schedule or example questionnaire provided	Allogeneic transplant – 72% short term oral complaints, 47% long term oral complaints Autologous transplant – 52% short term oral complaints, 17% long term oral complaints. Pre and post transplant 52% visited dentist to ensure mouth was fine 49% were aware of professional cleaning and 31% wanted OHI prior to hospitalisation 54% of dentists stated the patient's medical condition made treatment more difficult. Visiting a dentist (73% before, 77% after), how to brush teeth (77% before and 60% after) and using a fluoride rinse (50% before and after) were the 3 most important recommendations given by dentists.
(Braga-Diniz. J. et al. 2017) The need for endodontic treatment and systemic characteristics of hematopoietic	188 participants M:F = 114:74 Age: unknown Pre HSCT = 103	Retrospective study Medical records reviewed March 2011 – March 2016 Review the characteristics of HSCT and the need for endodontic treatment	The majority of participants were having HSCT for leukaemia. Potential for dental infections to have a negative impact on HSCT success 24.3% of participants required endodontic treatment pre-HSCT, 24.7% required endodontic treatment

stem cell transplantation patients **2-**	Transplant type Autologous:Allogeneic = 13:175		post-HSCT. Highlighting the need for dental assessment pre-HSCT and post-HSCT. Doesn't discuss reason for endodontic treatment as opposed to extraction
(Elad. S. et al. 2008) A decision analysis: The dental management of patients prior to hematology cytotoxic therapy or hematopoietic stem cell transplantation **2-**	Decision analysis looking at 40year old patients undergoing conditioning +/- HSCT Included patient with haem-oncology malignancies	Decision analysis – comparing met and unmet dental needs Literature review – 2 databases with multiple MESH headings. Literature was reviewed and outcomes placed in the decision tree.	Decision tree is used to estimate the likelihood of each outcome Choosing no dental evaluation increased the probability of 1.8 in every 1000 HSCT patients dying of dental infection Differences between the 2 groups were small, however decision tree showed that dental assessment and treatment are the preferred method. Didn't examine cost or quality of life for these patients
(Ertas. E.T. et al. 2014) Comparison of chemotherapy and hematopoietic stem cell transplantation pre and postterm DMFT scores: A preliminary study	36 subjects M:F = 27:6 Average age: 31.8 +/- 12.4 Allogeneic transplant: 34 Autologous transplant: 2	Pre HSCT subjects attended for dental assessment and treatment Post HSCT (6months) subjects were re-referred for a review DMFT – pre and post HSCT were recorded	Mean DMFT score was 7.0 pre-transplant and 8.3 post-transplant Pre HSCT 34/36 subjects and post-HSCT 29/36 subjects showed signs of dental pathology Percentage of decayed teeth was 7.9% pre HSCT rose to 8.9% post HSCT Significant increase in DMFT scores following HSCT – including increase in decayed teeth

2-			Highlights important of post-HSCT follow up.
(Gurgan. C.A et al. 2013) Periodontal status and posttransplantation complications following intensive periodontal treatment in patients who underwent allogeneic hematopoietic stem cell transplantation conditioned with myeloablative regimen **2-**	February 2004 – September 2010 – 202 subjects had a HSCT All these subjects had a pre-HSCT dental assessment and treatment. 3 months following HSCT subjects were invited back for review only 29 attended and were included in the study. (85.6% drop out rate) M:F =12:17 Average age: 32.45 +/- 8.44years PBSCT =14 subjects BMT =15 subjects	No controls Compared periodontal health pre-HSCT and post-HSCT Intervention = dental treatment including OHI, scaling, NSPT, restorations and extractions Periodontal values were recorded pre-HSCT, 3-4weeks after treatment and at 3 months post-HSCT including: plaque indices, gingival indices, pocket depths and bleeding on probing. Presence of acute GVHD, duration and severity of mucositis were also recorded.	Significant improvement in periodontal health post periodontal treatment and this was maintained 3months after HSCT Significant decreases in plaque and gingival indices along with BOP scores and pocket depths 15 subjects had acute GVHD, 12 subjects had mucositis. Alterations/decreases in bleeding on probing reversely related to presence of OM – the more BOP values improved = lower frequency of OM
(Masaya, A. et al. 2013) Myelosuppression grading of chemotherapies	37 subjects receiving treatment for haematological malignancies. M:F = 23:14. Age range = 23-70	Retrospective observational study Classified different chemotherapy regimens into groups based on the level of myelosuppression: Grade A = mild	No delays or alterations to the scheduled chemotherapy regimen 2 subjects experienced severe odontogenic infections 1 subject experienced sepsis associated with a dental extraction site.

for hematologic malignancies to facilitate communication between medical and dental staff: lessons from two cases experienced odontogenic septicaemia. **2-**	January 2009 – December 2010 Transplant = 14 subjects Chemotherapy alone = 23 subjects Autologous transplant = 4subjects Allogeneic transplant = 10 subjects	Grade B = moderate Grade C = severe Grade D = persistent myelosuppression Dental examination completed and removal of all unsalvageable teeth. Noted any odontogenic infections that occurred during chemotherapy or transplant period.	1 subject experienced sepsis due to advanced marginal periodontitis. Found that the grading used for chemotherapy regimens was a useful tool. Chemotherapy regimens of either grade B or C put patients at increased risk. Need for a prospective study with a larger sample size.
(Mawardi. H. et al. 2016) Hematopoietic Cell Transplantation in Patients with Medication-Related Osteonecrosis of the Jaws **3**	11 subjects M:F= 8:3 Age range: 46-71years December 2005 – December 2014	Retrospective Review of medical and dental records for patients undergoing HCT for MM with diagnosed MRONJ Record of Post HCT complications.	The incidence of post HCT complications – fever, positive blood cultures, length of hospital stay were comparable to Non-MRONJ patients MRONJ stage was not worsened by HCT
(Melkos. A.B. et al. 2003) Dental treatment prior to stem cell transplantation	58 subjects M:F= 36:22 Average age: 39.7years Allogeneic transplant: 52 subjects	Prospective study Control: no dental treatment Dental examination and treatment was carried out and then patients were followed	Post op complications in 48 subjects (27 group 1 and 21 group 2) 19 post op infections in 16 subjects (group 1 = 9, group 2 =7)

and its influence on the posttransplantation outcome **2+**	Autologous transplant: 2 subjects January – December 2000 2 groups 1. No treatment need/treatment complete (36 subjects) 2. No dental treatment provided (22 subjects)	up for complications (infection, mucositis, relapse, GVHD) for an average of 50.45weeks. Comparisons between both groups	No statistical association between dental foci impact and post-HSCT complications. Survival rate was unaffected between the groups
(Soga . Y. et al. 2008) Appearance of multi-drug resistant opportunistic bacteria on the gingiva during leukaemia treatment **3**	1 case presentation 53year old female AML Allogeneic: Umbilical cord stem cell transplant	Case report – 53year old female with AML. Pre-HSCT dental assessment identified mild generalised periodontitis with gingival hypertrophy however due to platelet and neutrophil count scaling of pockets could not be performed. Pocket irrigation with 0.2% povidone iodine daily and 2% minocycline gel was applied weekly. The patient had an elevated CRP pre- and during HSCT with elevated temperature.	No other systemic infection other than periodontitis was diagnosed in this patient before conditioning. Scaling and root planning prior to chemotherapy can reduce gingival inflammation Gingivae in patients undergoing HSCT can act as a reservoir for multi-drug resistant bacteria.

		7 days post HSCT white smears appeared on gingivae = *S.Maltophilia.* Patient died 14days post HSCT	
(Toro. J.J. et al. 2016) Edentulism and transplant-associated complications in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation **2+**	254 subjects 100% males Age range: 42-75years 45 subjects were edentulous 90 subjects were dentate 100% autologous transplant January 2003 – September 2012	Control: dentate subjects Retrospective Subject records were reviewed All subjects underwent a pre-HSCT dental assessment and treatment Recorded: age, gender, ethnicity, MM stage, time from diagnosis – HSCT, performance status, conditioning regime, complications during transplant (fever, oral mucositis, bacteraemia, diarrhoea, nausea/vomiting), neutrophil engraftment and duration of hospitalisation	No significant differences between the groups with regards to post-HSCT complications
(Yamagata. K. et al. 2006) A prospective study to evaluate a new dental	41 subjects M:F= 22:19 Average age: 41.3years 1998-2004	Prospective evaluation to develop new protocol Dental examination and treatments were recorded	38 subjects had dental pathology 36 subjects had dental treatment completed

management protocol before hematopoietic stem cell transplantation **3**	BMT = 28 subjects PBSCT = 13 subjects	along with post HSCT complications Aim of new dental protocol was to preserve teeth where possible. Only extracted retained roots, teeth with PA pathology where limited treatment time, teeth with severe periodontal involvement, P/E third molars with pericoronitis/suppuration	No subjects experienced odontogenic infections during HSCT Time limitations affect clinical decisions and completed dental treatment Intensive dental treatment is not necessary Treatment modality matched against severity of disease – only extract severely disease teeth. Early dental screening is essential and patients should be reassessed 1 month before if seen early. Suggestion that it is safe to observe periapical lesions <5mm
(Yamagata. K. et al. 2011) Prospective study establishing a management plan for impacted third molar in patients undergoing hematopoietic stem cell transplantation **2-**	84 subjects referred 35/84 had 1 or more impacted third molars enrolled M:F= 18:17 Average age: 32.1years BMT – 51 subjects PBSCT – 30 subjects Umbilical cord – 3subjects 2 groups Non ITM group ITM group 2000-2008	Prospective evaluation to develop new protocol All subjects had a dental assessment and appropriate dental treatment as necessary pre-HSCT Frequency of oral complaints and complications during the HSCT period were recorded	7/35 ITMs on 6 subjects were extracted due to symptoms (all mandibular) No subject showed signs of odontogenic infection during the HSCT period No significant difference between groups and duration of fever or number of days where WBC were <1000µL. Sepsis from oral mucositis – 2 in ITM group + 4 in non-ITM group No difference in median survival periods between the 2 groups however median number of days where WBC

			<1000µL for patients who died or survived was significant. Protocol to not to remove asymptomatic ITM appears not to increase risk of odontogenic infections during HSCT.

Post-HSCT complications

Author/ Title /**Level of Evidence**	Sample Characteristics	Study Design	Summary of Findings
(Barrach. R. et al. 2017) Oral changes in individuals undergoing hematopoietic stem cell transplantation **2-**	65 subjects Gender – unknown Age – unknown Transplant type: Autologous: Allogeneic= 31:34	Prospective longitudinal cohort study Patients were reviewed with regards to their oral health status – 20 days prior to HSCT, 7 days following HSCT and at 100 days post-HSCT Reviewed and quantatively scored with regards to caries, periodontal health, retained roots, mobile teeth, prosthesis and orthodontics, mucositis, infection experience	Highlight potential for retained roots, carious teeth, periapical pathology, periodontally involved teeth being reservoirs for infections. All patients had experience of mucositis at 7 days post-transplant. No patients experienced infections that were odontogenic in origin despite the fact that no evidence of dental treatment being provided prior to HSCT.
(Borbasi.S et al. 2002) 5 themes described the experiences of patients with chemotherapy induced oral mucositis	6 subjects M:F = 2:4 Age range = 38-63years Inclusion: autologous stem cell transplant	Qualitative Study Interpretive descriptive phenomenological study. Subjects underwent weekly indepth interviews (45mins-1hour) over 4weeks, then	Key themes that emerged: 1. Presence of nurses 2. Therapeutic interventions 3. Manifestations of mucositis 4. Distress of eating (and not eating) 5. Was the treatment worthwhile?

3	Exclusion: non-english speak, expected survival <3months	week 8 and week 12 or when their mucositis had resolved. Total of 19 interviews – recorded and transcribed verbatim Interviews explored subjects experiences of mucositis	Highlights the need for nurses to prepare the patients for the consequences of HSCT.
(Brand.H.S et al. 2009) Xerostomia and chronic oral complications among patients treated with haematopoietic stem cell transplant **2+**	48 subjects M:F = 19:29 Average age: 53.0 +/- 9.4years Autologous transplant – 11 subjects Allogeneic transplant – 33 subjects Autologous followed by Allogeneic transplant – 4 subjects Comparison group – 41 subjects M:F = 14:27 Average age: 51.1 +/- 9.1years	Control: partners of HSCT subjects All subjects completed the Dutch translation of the xerostomia inventory and an oral health questionnaire The results were then compared between the 2 groups	There were significant differences between all items explored in the xerostomia inventory between the HSCT group and the control. Greater severity of oral problems was found in the HSCT group No significant difference between HSCT group and control with regards to tooth sensitivity, broken/painful teeth or gingival bleeding. No significant difference between patients in the HSCT group receiving TBI than those who didn't. Those in HSCT who had received TBI reported increased altered taste 86% of allogeneic transplant reported GVHD affecting oral cavity and for these subjects mucosal pain was more severe

(Castellarin. P. et al. 2012) Extensive Dental Caries in Patients with Oral Chronic Graft-versus-Host Disease **2-**	21 participants with a diagnosis of cGvHD following HSCT M:F = 15:6 Average age = 45 (13-67 years) All allogeneic HSCT recipients	Retrospective case note review All patients had pre-HSCT dental assessment and definitive treatment Assessed post-HSCT with diagnosis of cGvHD and caries	19/21 diagnosed with oral cGvHD Review post-transplant occurred on average at 22 months 20/21 shows signs of salivary gland cGvHD Rampant caries was noted in 10 participants requiring extractions – this was higher than what was required pre-transplant Highlights the need for continued dental review and advice following allo-HSCT. The participants in this study had worse caries experiences post-HSCT with diagnosis of cGvHD and xerostomia.
(Da Silva Santos. P.S. et al. 2010) Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis **2+**	70 patients receiving HSCT for CML from 2 hospital sites SG – 35 patients who received dental treatment prior to HSCT CG – 35 patients who did not receive dental treatment prior to HSCT M:F unknown Average age unknown Transplant type unknown	Control: 35 patients who did not receive dental treatment prior to HSCT Following hospital admission all subjects were reviewed with regards to incidence, severity and time elapsed for oral mucositis	No statistical difference for incidence or severity of mucositis however SG had a shorter duration of mucositis than CG who did not receive oral care.

	Conditioning regimes were similar		
(Duncan. C. et al. 2015) Long-Term Survival and Late Effects among One-Year Survivors of Second Allogeneic Hematopoietic Cell Transplantation for Relapsed Acute Leukemia and Myelodysplastic Syndromes **2+**	325 subjects 146 children M:F= 92:54 179 adults M:F= 99:80 Average ages: unknown January 1980 – December 2009	Retrospective analysis of data contained in CIBMTR database of subjects who were alive and in remission a year following their second allogeneic transplant due to disease relapse. Data collected over 10 year period looking at late effects and complications	2 – 10year survival rates: Children = 83% - 55% Adults = 75% - 39% Disease progression or relapse = major cause of death Overall mortality due to GVHD 32%, organ failure 25%, infection 16% and secondary malignancy 5%. Acute grade 2-4 GVHD late effect in 46% adults and chronic GVHD late effect 75% adults Over 10years for adults late effects most common 13% avascular necrosis, 20% cataracts.
(Elad. S et al. 2011) A randomized controlled trial of visible-light therapy for the prevention of oral mucositis **1-**	June 2007- February 2009 20 subjects undergoing HSCT Group A (10 subjects) Exposed to visible light therapy (BB-VLT) and standard preventative prophylaxis M:F = 6:4 Age = 49.1 +/-16.91	Prospective randomised double-blinded study Group A – exposed to visible light therapy Group B – exposed to a placebo light device of a similar design. All light therapy was administered 5 times a week for 28days (or 21 days if no mucositis)	There was only a statistical significant difference in mucositis presentation on visit 3. A reduction of mucositis related pain was also significant at visit 3. No difference in patient satisfaction with the treatment. BB-VLT is a safe and effective device to use in the prevention of mucositis post-HSCT

	Group B (10subjects) 1 subject excluded (died) Exposed to placebo light and standard preventative prophylaxis M:F = 4:5 Age = 35.33 +/- 10.82	Patients and oral care provided were blinded to treatment groups Patients examined daily by a physician and weekly by a member of research team. Mucositis scores using WHO and OMAS grading Subjects graded pain using visual analog scale. Adverse events were recorded. Patient satisfaction survey was completed about the treatment.	Further studies are needed with a larger sample size.
(Elad. S. et al. 2008) Oral effects of non-myeloablative stem cell transplantation: A prospective observational study. **2+**	34 subjects Transplant type: Autologous = 9 (group 1) MAC allogeneic = 9 (group 2) RIC allogeneic = 16 (group 3) M:F / Average age Group 1: 8:1 / 39.2yrs Group 2: 5:4 / 35.0yrs Group 3: 8:8 / 35.4yrs	Prospective longitudinal observational study Recruitment period – September 2000 – June 2001 Patients oral mucosa was review every 2 weeks from 14 days post-HSCT to 100days aGvHD oral lesion was defined as oral ulceration	No statistical difference between prevalence of non-GvHD oral lesions between MAC and RIC regimes Prevalence of aGvHD oral lesions was statistically more in patients who received MAC There was no difference in the prevalence of opportunistic infections e.g candida.

		following the engraftment period.	
(Epstein. J. et al. 2008) Doxepin rinse for the management of mucositis pain in patients with cancer: one week follow up of topical therapy. **2-**	9 subjects M:F = 6:3 Age range: 25-61years Subjects having treatment for cancer including head and neck radiotherapy (6subjects), chemotherapy or HSCT (3subjects)	No controls Assess the impact of using doxepin over 1 week Subjects visited twice – at the start of the trial and the following week Doxepin (5mg/ml) suspension mixed with 1% alcohol and sorbitol Rinse 5ml for 1min – 3-6times per day as required (started from initial visit) Patients usual management of mucositis pain continued Level of mucositis was scored at each visit. VAS scores for oral pain were scored pre-rinse, then 5mins, 15mins, the hourly (to 4hours) following rinse.	Significant reduction of oral pain at 5mins and 15mins following the rinse Statistically significant reduction of pain on eating from after the rinse was administered at initial up visit and follow up visit Doxepin gives an extended duration of pain reduction Severity of mucositis, reduction of baseline pain over the week and reported side effects showed no statistical difference from baseline recordings.
(Filipovich. A. et al. 2005) National Institutes of Health consensus development project	No sample – report/review article	Expert opinion and review article No methodology described	Report has 3 main outcomes: 1. Standardises the criteria for diagnosis cGvHD

on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working groups report. **4**			2. Proposal of a new clinical scoring system to describe the severity of cGvHD 3. New guidelines on how to assess cGvHD
(Imanguli. MM. et al. 2008) Oral graft-vs-host disease **3**	No sample – review article.	Literature review Searches limited to MEDLINE/Pubmed databases. Limited to English language, peer reviewed journals. Searches looking at – GVHD patho-biology, salivary gland disease after HSCT, treatments for GVHD.	Describes patho-biology, oral presentation, histopathology and treatment. Describes difference between aGCHD and cGVHD – presentation as opposed to time. cGVHD difficult long-term challenge in allogeneic HSCT. Still need to develop effective therapeutic strategies. Similarity of cGVHD and other autoimmune disorders. Need further research in this field.
(Kashiwazaki. H. et al. 2012) Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with	140 subjects seen between February 2002 – December 2009, who underwent allogeneic bone marrow transplant 2 groups: Non-POHC (2002-2005) – 62 subjects – age	Retrospective analysis Recorded: Conditioning regimes Grade of mucositis – WHO classification Febrile neutropenia – where temperature >37.5’ and neutrophils $<0.5x10^9/L$	Incidence of mucositis in POHC group was 66.7% compared to 93.5% in non-POHC group. Incidence of febrile neutropenia and CRP levels were also lower in POHC group.

allogeneic bone marrow transplant **2+**	range: 15-66years. M:F = 32:30 POHC (2006-2009) – 78 subjects – age range: 18-77years. M:F = 44:34	Professional oral health care (POHC) was only given from 2006 onwards; included toothbrushing, interdental cleaning, and use of a wet sponge when complained of dry mouth.	Multivariate analysis showed POHC was significantly associated with mucositis incidence.
(Katz. J. et al. 2014) Oral squamous cell carcinoma positive for p16/human papilloma virus in post allogeneic stem cell transplantation: 2 cases and review of the literature **3**	2 cases Both male Case 1 – 68yrs, allo-HSCT for B cell lymphoma 22 yrs previous Case 2 – 18yrs, allo-HSCT for AML 9 yrs previous.	2 case reports presenting a number of years after allo-HSCT with SCC. Following histopathology both specimens were strongly reactive for p16/HPV	Recommend long-term surveillance for allo-HSCT recipients particularly with a diagnosis of cGvHD. Question whether HPV screening is indicated.
(Khouri.V. et al. 2009) Use of therapeutic laser for the prevention and treatment of oral mucositis **2+**	22 subjects March 2004 – September 2006 Ethics achieved Allogeneic HSCT Group 1 (12) (treatment):	Randomised control trial Randomisation according to hospitalisation. Differing conditioning regimes amongst subjects however all myeloablative.	Group 1 had a lower frequency and severity of OM – statistically significant No clinical difference in the presence of erythema between the groups Size of the lesions present were greater in group 2

	M:F = 10:2 Age = 32.7 Group 2 (10) (control) M:F = 7:3 Age = 27.5 Inclusion: >12yrs, haematological/haem-oncological disease, myeloablative conditioning regime, allogeneic HSCT.	Both groups underwent the same prevention protocol for mucositis Group 1 = treatment group. "Mucositis Formula" mouthrinse, oral hygiene protocol and laser treatment. 2 lasers used on alternate days once a day. Questionnaire about the laser completed at the end of treatment. Group 2 = control group. Conventional mouthwash and oral hygiene protocol only. Study was not blinded as group 2 were not "treated" with a sham laser. Interventions were continued until day 15 post-transplant or if engraftment was observed prior to this the interventions were stopped. OMAS and WHO scale to measure mucositis present.	Laser treatment can be an effective option in the treatment and prevention of oral mucositis Further research is required.

(Laaksonen. M. et al. 2011) Longitudinal assessment of haematopoietic stem cell transplant and hyposalivation **2+**	228 allogeneic HSCT recipients (2002-2009) M:F = 134:94 Average age: 43years Control group = 141 healthy individuals (no medications) M:F = 69:75 Average age: 46years	Control = healthy individuals CG – stimulated saliva flow measured on one occasion HSCT group – grouped due to diagnosis, dose of TBI (no-TBI, low dose TBI, high dose TBI) and conditioning regime stimulated saliva flow measured pre-HSCT, 6 (109 subjects),12(99 subjects), 24 months (76 subjects) following HSCT Stimulated saliva – first to chew on wax for 1min whilst swallowing saliva then to chew on wax for 5mins whilst saliva collected.	Hyposalivation was common amongst HSCT group – 40% pre HSCT, 53% 6months, 31% at 12months and 26% at 12months. CG 16% had hyposalivation Pre-HSCT females demonstrated increased frequency of hyposalivation than males Severe hyposalivation was seen particularly at 6months – 18% HSCT group 40% of subjects died during this period in whom hyposalivation was more common. Patients having TBI showed increased hyposalivation pre-HSCT and at 6months Recovery of stimulated saliva with time.
(Legert K.G. et al. 2014) Reduced intensity conditioning and oral care measures prevent oral mucositis and reduces days of hospitalisation in	171 subjects undergoing allogeneic HSCT (161 subjects treated for malignant disease) October 2007- May 2011 Age range: 12-71years MAC = 72 subjects, M:F= 36:36	Comparative between MAC and RIC regimes Baseline dental examination and treatment During observation period; nursing staff examined for oral mucositis (OM) from 3days prior to 25day post HSCT – WHO criteria.	86% of subjects developed OM MAC significantly higher total OM score from days 9-12 than RIC Use of Bulsulfan increased WHO OM score on days 9-12 TBI didn’t influence severity or incidence of OM

allogeneic stem cell transplant participants. **2-**	RIC = 99 subjects, M:F= 55:44	3xweekly dentist/hygienist examined oral cavity for OM using OMAS VAS and NCI-CTCAE used to record pain in the oral cavity Oral function and salivation was discussed with the patient daily	Year of HSCT had an effect on severity of OM, introduction of oral care protocol in 2011 Significant correlation between higher OM score on days 13-24 and length of hospitalisation
(Lew. J. et al. 2007) Mucosal graft-versus-host disease **4**	Review paper	No sample – review article	Discusses – pathophysiology and types of GvHD along with its treatment.
(Mauramo. M et al. 2017) Determinants of stimulated salivary flow among haematopoietic stem cell transplantation recipients **2-**	118 subjects M:F = 66:52 Age = 49.3 (22-74) Autologous HSCT: 27 subjects Allogeneic HSCT: 91 subjects TBI: 59 subjects Myeloablative conditioning: 66 subjects Control group = 247 subjects M:F = 106:141 Age = 43 (22-74)	Prospective longitudinal study – case control Patients receiving HSCT had stimulated salivary flow measured: • Post-conditioning (Pre-HSCT) (118) • 6months post HSCT (102) • 12months post HSCT (95) Any changes to medications were noted. Control group – healthy volunteers with no medications. Stimulated	Hyposalivation was more frequent at each interval among the HSCT group compared the controls Females had slightly lower stimulated salivary flow rates than males Stimulated salivary flow rates improved with time and were higher 12months post-HSCT Antivirals, antifungals, antacids, antineoplastics and immunosuppressants, antibacterials, corticosteroids, cardiovascular drugs, antiemetics, anxiolytics and antidepressants were the most

		salivary flow rate measured once. Stimulated salivary flow rate <0.7ml/min = hyposalivation	common drugs post HSCT but did not significantly impact on SWSFR Hyposalivation is a multicausal phenomenon All subjects receiving HSCT should be considered high risk of hyposalivation.
(Mays. J.W et al. 2013) Oral chronic graft versus host disease: current pathogenesis, therapy, and research **4**	Review article – no sample	Review article based on literature review and expert opinion No methodology of literature review stated. Keywords stated.	Highlights general and systemic features of general and oral GVHD 50% of patients who survive 1year post-HSCT develop the disease. 5year mortality rate for cGVHD patients = 70% Oral cavity = second most common organ involved – mucosal lesions, salivary gland disease, restricted mouth opening, secondary malignancies Increased risk of oral pain, dental caries Negative impact on speech, nutrition, eating and QoL NIH consensus report – clinical scoring Importance of early detection, diagnosis, management and regular follow up.

(Meier.J. et al. 2011) Oral chronic graft versus host disease: report from the International Consensus Conference on clinical practice in cGVHD **4**	No sample – review article with expert opinion	Review article No methodology for literature review Literature and guidance were graded as to the publication by the expert panel and then reviewed. Expert panel consisted of an oral medicine specialist, a dentist, 2 haematologists and an epidemiologist	Symptoms of cGVHD present within 2years post-HSCT. Usually preceded by aGVHD. Presentation of oral lesions, hyposalivation and secondary malignancies. Describes NIH clinical scoring scale Need for regular dental assessment, importance of good oral hygiene, possible restriction of mouth opening due to fibrosis. Risk of BRONJ in patients receiving bisphosphonates for multiple myeloma Need for interdisciplinary working
(Nappalli. D. et al. 2015) Oral manifestations in transplant patients **4**	Review article – no sample	Review article No method stated for literature review Key words stated	Oral cavity is a potential source of sepsis in immunocompromised patients Infections in the oral cavity may be suppressed or exaggerated due to decreased inflammatory response Recipients of matched unrelated/mismatched allogeneic transplants are at increased risk of infections. Increased risk of gingival overgrowth due to immunosuppressive drugs

			Presentation of oral mucositis, GVHD, xerostomia and secondary malignancies.
(Patussi. C. et al. 2014) Clinical assessment of oral mucositis and candidiasis compare to chemotherapeutic nadir in transplanted patients **3**	Subjects attending for HSCT January – December 2012 31 subjects M:F = 15:16 Age = 43.8 (19-66years) Autologous: 28 subjects Allogeneic: 3 subjects	Observational study Prospective Ethics and informed consent achieved Blood tests were performed daily on all subjects Mucositis was evaluated with the WHO scoring system Low frequency laser application was used at least twice weekly on all subjects All subjects used chlorhexidine mouthwash 0.12% to support oral hygiene Comparisons were made between tobacco use, diagnosis, type of transplant, use of oral prosthesis	Chemotherapeutic nadir is the period where following chemotherapy the cell count decreases rapidly. Prescence of mucositis was no associated with the counting of leukocytes Decrease in leukocytes found between day 2 -8 No difference in presence of mucositis between allogeneic and autologous transplants No patients presented with candidiasis Patients who reported low tobacco consumption presented with more severe mucositis Low frequency laser treatment can be effective in treating and preventing mucositis
(Petti.S. et al. 2013) Orofacial diseases in solid organ and haematopoietic stem	Review article - No sample	Review article Searches limited to MEDLINE – observational studies and cases series were assessed. Keywords listed.	Oropharyngeal cancer is the most common in HSCT recipients Oral cancer is significantly associated with cGVHD

cell transplant recipients. **4**		Strength of association between the literature was agreed by the four authors	cGVHD is the leading cause of mortality in HSCT recipients Definition of aGVHD and cGVHD GVHD is associated with the HLA mismatch of donor and recipient Mucositis is a frequent toxicity in myeloablative or TBI conditioning regimes Oral infections in HSCT recipients – bacteraemia, fungal infections (candida, aspergillous), HSV, CMV, VZV. Oral infections are often proceeded by mucositis Need for pre- and post- HSCT dental review.
(Santos-Silva. A.R et al. 2015) cGVHD-Related Caries and Its Shared Features with Other 'Dry-Mouth'-Related Caries **3**	5 cases M:F= 3:2 Age range: 14-47years All subjects underwent allogeneic transplant	Series of case reports All subjects underwent pre-dental assessment prior to HSCT. However developed chronic GVHD as a consequence. Dentally they suffered with extensive caries as a consequence	Importance of continuing review of patients who have undergone a HSCT particularly if they have cGVHD Links of GVHD and xerostomia leading to rampant caries
(Sonis. S.T. et al. 2001) Oral mucositis and the clinical and economic	92 subjects M:F = 40:60 (%)	Piolet observational prospective study	Found that the severity of OMAS is significantly correlated with: • Days of injectable narcotics, TPN and injectable antibiotics

outcomes of hematopoietic stem cell transplantation **3**	Age = 44.5 (+/- 10.6) Transplant type: Allogeneic = 50 Autologous = 42	Subjects were assessed for oral mucositis (OMAS score) from day 1 of conditioning and continuing for 28 days. OMAS score was compared against other outcomes: 1. No. febrile days 2. Incidence of infection 3. No. days received TPN 4. No. days received injectable narcotics 5. No. days spent in hospital within 60 days from 1st day of conditioning 6. Total hospital charges 7. Mortality within 100 days	• Risk of significant infection • Increased hospital days and therefore charges • Increased risk of mortality Peak mucositis scores were higher in allograft patients. However mucositis was found to be a more important risk factor for autograft patients.
(Sonis. S.T. 2009) Efficacy of palifermin (keratinocyte growth factor-1) in the amelioration of oral mucositis **3**	No sample – review article	Systematic review article Key word search of 2 databases Reviewed 100 papers and 4 abstracts – only 12 papers and 3 abstracts were included for analysis	Patients receiving myeloablative conditioning particularly TBI are at >50% risk of mucositis. Level 3 evidence supports the use of palifermin in treating mucositis in allograft recipients. Level 2 evidence supports the use of palifermin in treating mucositis in autograft recipients.
(Stoopler. E. 2013)	1 case presentation 50year old female	Patient presented with painful mucosal lesions 8 months	Topical corticosteroids can be helpful in the treatment of cGVHD.

Management of oral chronic graft-versus-host disease **3**	Unspecified leukaemia Allogeneic HSCT	post-HSCT. Diagnosed with vaginal GVHD by gynaecologist. Diagnosis of cGVHD made. Treatment with: topical dexamethasone rinse, topical betamethasone gel and nystatin oral suspension. At 1 month review lesions, had resolved and masticatory function returned.	
(Torres-Pereira. C.C. et al. 2014) Oral squamous cell carcinoma in two siblings with Fanconi anemia after allogeneic bone transplant **4**	2 cases M:F = 0:2 Case 1 – 18year old female with Fanconi anemia and treatment with allogeneic HSCT. Case 2 – sibling of case 1 (donor for case 1). 28 year old female with Fanconi anemia, treatment with allogeneic HSCT	Both cases developed cGVHD following allogeneic HSCT. They then preceded to present with squamous cell carcinomas in the oral cavity which required treatment.	Consideration to long term oral surveillance following allogeneic HSCT especially in patients who develop cGvHD or have an initial diagnosis of Fanconi anemia.
(Tsushima. F. et al. 2015)	1 case Male	Case report	Recognition of long term complications of HSCT.

A case of upper gingiva carcinoma with chronic graft versus host disease after allogeneic bone marrow transplant **3**	51years Allogeneic stem cell transplant 22years ago for AML	Subject developed cGVHD following HSCT 22years following HSCT developed squamous cell carcinoma left palatal gingivae.	Solid tumors are a consequence of GVHD
(Villa. A. et al. 2015) Mucositis: pathobiology and management **4**	Review article	Review article No structured methodology stated.	Describes pathobiology and management of mucositis 60-85% of patients receiving HSCT will experience mucositis. Following HSCT mucositis tends to present at day 3 or 4 and peaks at days 7-14 then proceeds to resolve. Describes current drugs that can reduce the severity and duration of mucositis. Advises future studies should be around the effect of drug therapies on patients who are genetically predisposed.
(Yuan. A. et al. 2016) Oral chronic GVHD outcomes and resource utilization: a subanalysis from the	79 patients across 5 oral medicine or transplant centres (2 oral medicine centres) March 2012 M:F = unknown	Retrospective data analysis (as part of the GVHD cohort study 2007) To compare current practice of diagnosis and treatment with NIH consensus guidance	Ancillary topical therapies were prescribed to over half of patients Additional ancillary topical therapies were prescribed more often at oral medicine centres (52%)

chronic GVHD consortium **3**	Age = 50years (11-71) Diagnosis of chronic GVHD	Clinical or histological diagnosis of GVHD was accepted Both patient and clinician measures of severity and impact of oral cavity changes were assessed. Study member at each site collected the data Data collected at each visit = date, provider type, systemic immunosuppressive medications, and ancillary therapies	Patients treated with topical therapies were 5 times more likely to have NIH mouth pain = oral cavity score >1. A positive score on pain or function prompted management more than clinical assessment of lesions Data was consistent with current guidance
(Weng. X. et al. 2017) Multiple and recurrent squamous cell carcinoma of the oral cavity after graft-versus-host disease **3**	1 case 42 year old male patient – allo-HSCT for AML Diagnosed with cGvHD Presented with multiple SCCs 5 years post HSCT	Case report	Importance of continued surveillance post-HSCT and GvHD diagnosis Need for multi-disciplinary team involvement in their diagnosis and treatment.

HSCT and oral health related quality of life

Author/ Title /**Level of Evidence**	Sample Characteristics	Study Design	Summary of Findings
(Bezinelli. L. et al. 2016) Quality of life related to oral mucositis of patients undergoing haematopoietic stem cell transplantation and receiving specialised oral care with low-level laser therapy: a prospective observational study) **3**	69 subjects over a 2 year period M:F = 46:23 Type of transplant Autologous = 35 Allogeneic relative donor = 14 Allogeneic unrelated donor = 20 No control group	Observational prospective study WHO grading system used to grade the severity of mucositis OHIP-14 and PROMS scales used to assess the patient reported QoL All patients received treatment with LLLT for their mucositis from day 1 post-HSCT. QoL was measured at: 1. Prior to HSCT 2. 5th day for autologous and 8th day for allogeneic post-HSCT 3. At bone marrow integration 4. 30 days post-discharge.	All patients scored the worst on OHIP and PROMS at time 2 (5/8 days post HSCT). QoL improves over time in patients receiving LLLT for treatment of mucositis.

(Depalo, J. et al. 2015) Assessing the relationship between oral graft-versus-host disease and global measures of quality of life. **2+**	569 subjects from 9 participating study centres. M:F = 329:240 Age = unknown Diagnosis = incident GvHD (diagnosed <3months post HSCT) or prevalent GvHD (diagnosed >3 months but <3 years post-HSCT) 340:229	Prospective multicentre observational study. QoL assessment using FACT-BMT and SF-36. Subjects were classified into three groups depending on their presentation of GvHD 1. Isolated oral involvement 2. Concomitant extra-oral involvement 3. Only extra-oral involvement Differences in QoL were assessed between the groups.	No meaningful difference in QoL scores between the three groups Overall disease severity was higher in the concomitant extra-oral involvement and the only extra-oral involvement groups. Further work is required on the impact of oral health related quality of life in patients with oral GvHD.
(Silva. L. C. et al. 2015) The impact of low-level laser therapy on oral mucositis and quality of life in patients undergoing hematopoietic stem cell transplantation using the oral health impact profile and functional assessment	39 subjects M:F = 17:22 Age = 39 (14-63years) Transplant type Autologous: Allogeneic = 24:15 Control group = 19 subjects	Randomised, controlled and double blinded clinical trial – a pilot study. Comparing the quality of life of subjects with mucositis who have LLLT compared to those who do not. QoL questionnaires – FACT-BMT and OHIP-14	QoL between the two groups was at its lowest at day 7 post-HSCT There was no difference in reported QoL scores between the control group and the study group. LLLT can improve the clinical presentation and severity of oral mucositis.

of cancer therapy – bone marrow transplantation questionnaires. **1-**	Study group = 20 subjects	Study group received LLLT from day 1 post-HSCT to day 7 post-HSCT at 10 points around the mouth. QoL was assessed at admission, day 7 post-HSCT and at discharge.	
(Tinoco-Araujo. J. et al. 2015) Oral health-related quality of life before hematopoietic stem cell transplantation. **2-**	200 subjects Control group (CG) = 100 subjects Study group (SG) = 100 subjects CG = healthy volunteers SG = subjects having autologous or allogeneic HSCT CG: M:F = 62:38 SG: M:F = 61:39 Transplant type: unknown	Prospective observational cohort study CG and SG underwent dental assessment – underlying disease, dental and periodontal conditions OHIP-14 questionnaire was completed to assess oral health-related quality of life.	There was found to be a weak impact of oral health on QoL in both groups. A significant impact of oral health on QoL was seen in patients with severely compromised teeth – in the domains of discomfort, psychological disability and deficiency. Recommends pre-HSCT dental assessment.

7.7 Appendix 7: SIGN levels of evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

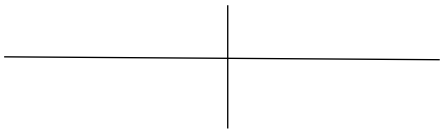
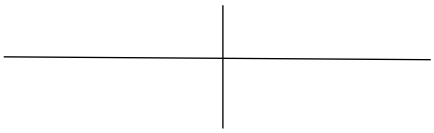
(Scottish Intercollegiate Guidelines Network, 1999-2012)

7.8 Appendix 8: Study groups

The types of patients who will be included in each different study group defined by the type of dental intervention received.
Dental intervention received
Group 1
• Patients who received comprehensive dental care – provision of all dental treatment required. Patient is dentally fit at time of transplant.
Group 2
• Patients who received solely extractions and dressings (temporary restorations).
Group 3
• Patients where no dental treatment was advised pre-transplant other than prevention advice
Group 4
• Patients who refused the dental treatment offered and received preventative advice.
No dental intervention received (control group)
Group 5
• Patients who were not referred for dental assessment due to time constraints, prognosis or refusal to be referred. • Patients who had a dental assessment but refused the dental treatment offered, and did not receive preventative advice. • Patients who are edentulous (these patients are not currently referred).

7.9 Appendix 9: Data collection form

Unique ID				
Gender		Postcode (first part of code MAX 4 digits)		
Age		Occupation		
Comorbidities				
Medications				
Social History	Smoker	Y / N	No. _____	
	Alcohol	Y / N	Units _____	
	Other			
	BMI:	Weight pre HSCT:		
Date of initial diagnosis				
Haematological Diagnosis				
Disease Classification (including genetic abnormalities)				
Haematological treatment to date				
Predisposing Condition				
Previous HSCT:	Yes	No		
Proposed date of transplant				

Date of dental referral				
Date of Dental Assessment				
GDP	Yes / No			
Previous attendance	Regular / Irregular			
Dental Findings	Oral Hygiene			
	Mobile teeth			
	Carious teeth			
	Retained roots			
	BPE score: Recorded			
	  Not Recorded			
	Other pathology			
Dental Treatment completed Date of appointments:	Oral Hygiene advice			
	Prescription			
	Extractions			
	Restorations			
	Periodontal treatment			
	Other treatment			
Outstanding Dental Treatment	Yes No Refused treatment			
Review of healing	Y / N	Date(s)		

Date of transplant			
Delayed	Yes	No	
	Reason:		
Status at HSCT	Primary induction failure	Complete haematological remission	Relapse ___ /___ / ____
Preparative regimen	Yes	No	
	Myeloablative:		
	Yes	No *(reason)*	
	Drugs:		
	Unknown	No	Yes *(list)*
	TBI:		
	No	Yes Total dose _____Gy No. fractions _____ No. days _____	
Type of transplant	Bone Marrow	Peripheral Blood	Core Blood
Quality of match	HLA – identical sibling	Syngenetic	HLA – matched other relative
	HLA – mismatched other relative	Unrelated donor	
GVHD prophylaxis	Yes *(list)*	No	
Survival status at HSCT (day 0)	Alive	Dead *(date)* ____ / ____ / ____	Died b/n preparation and HSCT *(date)*

			____ /____ / _____
	Main Cause of death:		
	Contributory Causes of death:		
Mucositis Yes No	Score:	Date:	Tx:
	Score:	Date:	Tx:
	Score:	Date:	Tx:
	Score:	Date:	Tx:
Duration of mucositis			
Neutropenic Sepsis Yes No	Organism:	Date:	Tx:
	Organism:	Date:	Tx:
	Organism:	Date:	Tx:
	Organism:	Date:	Tx:
Xerostomia Yes No	Date:	Tx:	
	Date:	Tx:	
	Date :	Tx:	
	Date:	Tx:	
Infection (bacterial, viral, fungal) Yes No	Date:	Stage:	Tx:
	Date:	Stage:	Tx:
	Date:	Stage:	Tx:
	Date:	Stage:	Tx:
Acute GVHD Yes No	Date:	Stage:	Tx:
	Date:	Stage:	Tx:
	Date:	Stage:	Tx:
	Date:	Stage:	Tx:

Feeding Regime	Oral feeding solids			
	Oral feeding thickened fluids			
	Nasogastric tube			
	Peg fed			
Absolute neutrophil count recovery	Yes *(date)*	No *(last assessed)*	Never below	Unknown
Platelet reconstitution (>20x10*9/L)	Yes *(date)*	No	Never below	Unknown
Early Graft Loss	No	Yes	Unknown	
Length of hospital stay (days)				
BMI on discharge:	Weight on discharge:			
Survival status at 100 days post-HSCT	Alive	Dead *(date)* ____ / ____ / ____		
	Main Cause of death:			
	Contributory causes of death:			
Chronic GVHD between HSCT – 100 days (date of death)	Yes *(date of diagnosis)* ____ / ____ / ____	No	Unknown	
Survival Status at Annual Follow up	Alive	Dead (date) ____ / ____ / ____		
	Main cause of death:			
	Contributory causes of death:			

7.10 Appendix 10: FACT-BMT questionnaire

FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-BMT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-BMT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The side effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

7.11 Appendix 11: Lee cGvHD symptom score

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

7.12 Appendix 12: OHIP-14 quality of life questionnaire

ORAL HEALTH IMPACT PROFILE

Name	Date

		HOW OFTEN have you had the problem during the last year? (circle your answer)					
1.	Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
2.	Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
3.	Have you had painful aching in your mouth?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
4.	Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
5.	Have you been self conscious because of your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
6.	Have you felt tense because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
7.	Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
8.	Have you had to interrupt meals because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
9.	Have you found it difficult to relax because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
10.	Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW

	HOW OFTEN have you had the problem during the last year? (circle your answer)					
11. Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
12. Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW
14. Have you been totally unable to function because of problems with your teeth, mouth or dentures?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW

CARE PLANNING: *If the person answered very often, fairly often or occasionally on any question, determine the* **Oral Health-Related Quality of Life** *most appropriate oral and general health intervention(s):*

Completed by
(name & professional designation)

INSTRUCTIONS

THE QUESTIONNAIRE.
This questionnaire asks how troubles with your teeth, mouth or dentures may have caused problems in your daily life. We would like you to complete the questionnaire even if you have good dental health. We would like to know how often you have had each of the 14 listed problems during the LAST YEAR.

HOW TO ANSWER THE QUESTIONS.
Each question on the left hand side of the page asks you about a particular dental problem. You should think about each question in turn, and circle the answer to the right of the question, to indicate how often you have had the problem during the last year.

EXAMPLES *If you occasionally had painful aching in your mouth, you would circle the answer as shown in this example.*

3. Have you had painful aching in your mouth?	VERY OFTEN	FAIRLY OFTEN	OCCAS-IONALLY	HARDLY EVER	NEVER	DON'T KNOW

OHIP Development: Slade GD. Derivation and validation of a short-form oral health impact profile. Community Dentistry & Oral Epidemiology 1997; 25:284-90.
OHIP Summary Scoring: Slade GD, Nuttall N, Sanders AE, Steele JG, Allen PF, Lahti S. Impacts of oral disorders in the United Kingdom and Australia. Br Dent J. 2005 Apr 23;198(8):489-93.

7.13 Appendix 13: Sample framework

Sample Framework

Age
>18years

Occupation
Professional
Manual Classes
Unemployed

Gender
Male
Female

Diagnosis
ALL
CLL
Lymphoma

Ethnicity

Graft Type
Allogeneic

Language
English

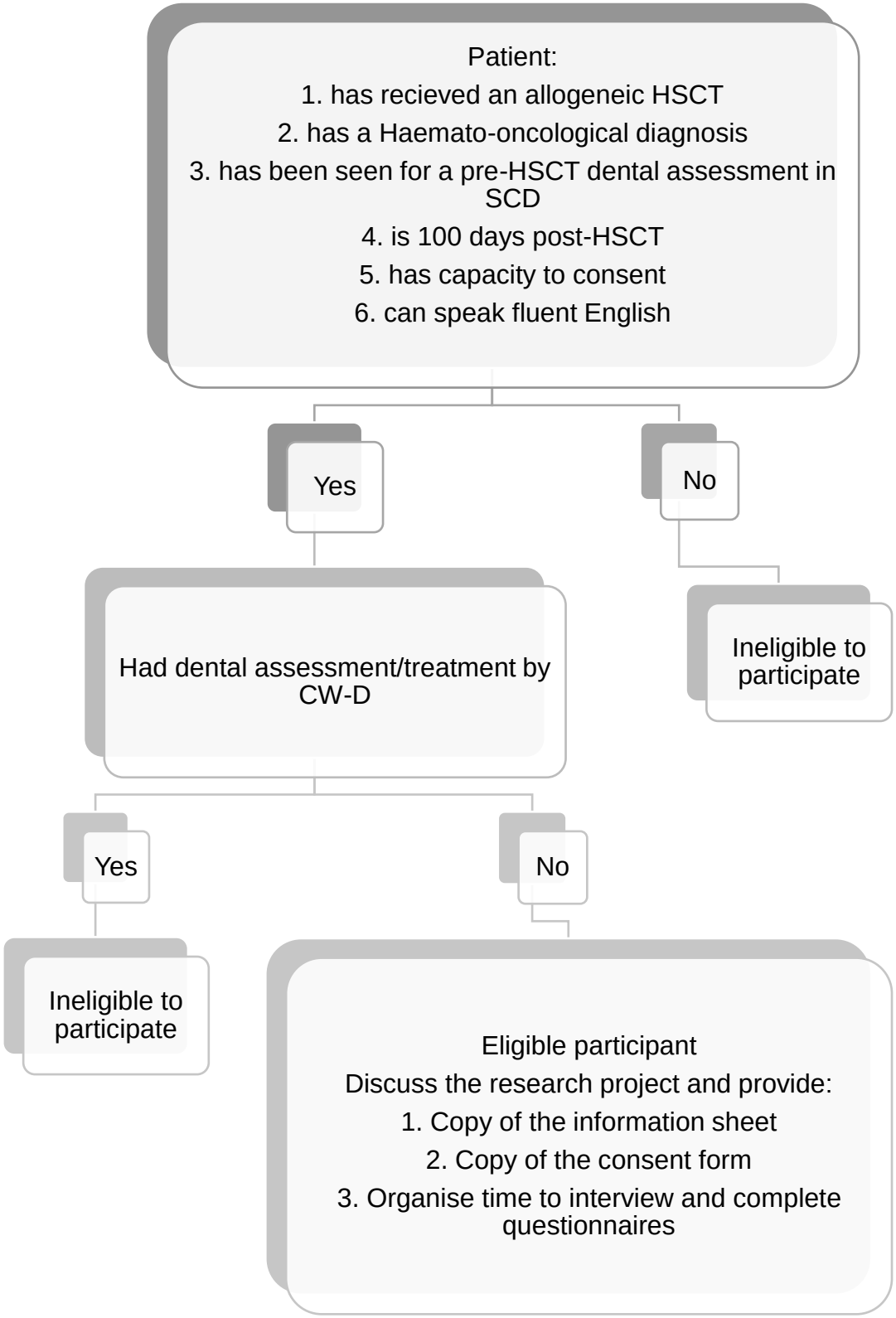
Treatment
RIC/TBI
Chemotherapy
BMT/PBSCT/UCSCT
Donor match
Failed HSCT

Marital Status
Single
Married/Cohabiting
Divorced/Widowed

Dental
Advice only
Extractions only
Comprehensive care

Children
Yes
No

7.14 Appendix 14: Eligibility framework



7.15 Appendix 15: Invitation to participate letter

Title:

Exploring patient views of the influence of the dental intervention received prior to allogeneic stem cell transplantation on their post-transplant outcomes.

Invitation paragraph

Clatterbridge Cancer Centre would like to invite you to take part in a research study. Before you decide it is important to understand why the research is being done and what it will involve. Please take the time to read the following information and ask any questions that you may have about what this research involves. We would be grateful if you could kindly take the time to consider this study and decide whether you wish to take part. Thank you.

Purpose of study

This study is being carried out as part of a research degree (DDSc in Special Care Dentistry) within the University of Liverpool.

Currently, there is a link between the Special Care Dentistry Department at Liverpool University Dental Hospital and the Stem Cell Transplantation and Cellular Therapy Unit at Clatterbridge Cancer Centre -

Liverpool. This link provides the opportunity for patients to have a dental assessment and treatment prior to their haematopoietic stem cell transplant.

From the study we are hoping to gain information about patients' views of this on the influence of dental assessment and/or treatment on patient outcomes following stem cell transplant, along with patient views on the service currently provided.

This study will focus on patients' who have had an allogeneic stem cell transplant.

Why have I been invited?

You have been invited to take part in the study as you have experienced the dental service provided by the Special Care Dentistry Department prior to your allogeneic stem cell transplant. You are now over 100 days post-transplant, and so may have experienced the potential post-transplant complications that can affect your mouth. The stem cell transplant team also feel that medically you are able to take part in this study.

Do I have to take part?

It is entirely up to you if you decide to take part in the study. The study will be fully explained to you and please ask any questions that you may have about the study.

What will happen if I do not take part?

If you refuse to take part of withdraw from the study at any point, and any information you have provided up to that point will be destroyed.

Refusal to take part or withdrawal from the study will not have any impact on your current and ongoing dental and medical care.

What will happen if I do decide to take part?

If you would like to take part then please contact the dental research student (via email clwd2701@liverpool.ac.uk) and arrange a suitable time for the interview to take place. The attached consent form will need to be completed and brought with you to the interview appointment, don't worry if you forget it spares will be available. If you do not have access to email/the internet and are interested in taking part please inform someone at the clinic.

The interviews will take part within an office in the Stem Cell Transplantation and Cellular Therapy Unit (CCC), Liverpool. Ideally the interview will follow one of your review appointments with the stem cell transplant team however if this is not possible then a further interview appointment can be scheduled or a telephone interview can be arranged.

Prior to the interview you will be asked to complete 3 quality of life questionnaires around your bone marrow transplant, GvHD symptoms and your oral health. Following completion of the questionnaire then a face-to-face interview lasting up to 1 hour will be completed. The interview will be recorded on to a recording device. You can stop the interview at any point.

The risks of taking part?

Taking part in the interview will mean giving up some of your free time; following your review appointment, having a further trip to the hospital or speaking on the telephone.

In addition, the interview process will ask questions on your experience of the dental service but also about the transplant process. It is appreciated that some people may find discussing this period stressful and emotional.

If you would like advice about whether or not to participate, please discuss this with the researcher or a member of the stem cell transplant team.

Benefits of taking part?

Participation in this study allows you to discuss your views and experiences of the dental service and the allogeneic transplant process. In addition, it allows you to express your views on the service and the information gained may help future recipients of stem cell transplants.

What if there is a problem?

If there is a problem prior to the interview appointment, please contact the main researcher to identify a solution.

If there is a problem during the interview, the interview will be stopped in order to seek a resolution of the problem. Having the interview within the Stem Cell Transplantation and Cellular Therapy Unit (CCC), allows contact and support from staff if required.

Will my details be kept confidential?

Yes, legal and ethical policies are in place to ensure that all information provided remains confidential. A master document detailing all

the participants of the study will be stored on a password protected trust computer.

Following the interview, the information will be written up onto a word document. The document will only include your initials, age and diagnosis allowing complete anonymity. Once the interviews are documented then the recording will be deleted.

What will happen to the results of the study?

The results of the study will be written up as part of a research degree and will be published in a peer-reviewed journal with either a Haematology-oncology or dental focus. However, given anonymity and confidentiality, you will not be identifiable from the reports or publications.

What if I need to complain?

If you have any concerns about the way the study has been conducted please contact the main researcher, who will try to answer your query. If you are still unhappy, then details of the complaints process can be provided to you.

Who is sponsoring the research?

The research is being sponsored by Clatterbridge Cancer Centre and has received ethical approval on 17/04/18.

Further information and contact details?

Researcher:	Supervisor:
Charlotte Wilson-Dewhurst	**Dr Amit Patel**
Academic Clinical Fellow in Special Care Dentistry	Consultant and Senior Lecturer in Stem Cell Transplantation and Intensive Care Medicine
Special Care Dentistry Department	Clatterbridge Cancer Centre Liverpool
Liverpool University Dental Hospital	Royal Liverpool University Hospital
Pembroke Place	Pembroke Place
L3 5PS	Liverpool

7.16 Appendix 16: Consent form

NHS
The Clatterbridge Cancer Centre
NHS Foundation Trust

IRAS ID: 224849

Study Number:

Participant Initials:

Participant Age:

Participant Diagnosis:

Contact telephone number:

Consent form

Title: ***Exploring patient views of the influence of the dental intervention received prior to allogenic stem cell transplantation on their post-operative outcomes.***

Name of Research Student: ***Charlotte Wilson-Dewhurst***

(Please tick box)

1	I confirm that I have read the participant information sheet (Version____, Dated__/__/__) for the above study. I have been able to ask questions and received satisfactory answers.	☐
2	I understand that my participation is voluntary and am free to withdraw at any time.	☐
3	I understand that if I choose to withdraw from the study that this will not affect my on-going medical care and any information I have already provided will be destroyed.	☐

4	I understand that the information I provide during the interviews will be shared with the clinical team, as part of a research project and written up and published in peer-reviewed journals.	☐
5	I understand that I will not be identifiable from the published information and I am happy for my initials, age and diagnosis to be used.	☐
6	I understand that the information I provide will be used to support future research and potentially make changes in the provision of clinical care.	☐
7	I agree to take part in the study.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Please provide any additional information in the space below:

7.17 Appendix 17: Topic guide

Title: A thematic analysis to explore patient views of the care pathway between Haematology and Special Care Dentistry and its influence on their quality of life.

Introduction

"Good morning/ afternoon, my name is Charlotte, I am a qualified dentist but I am now completing specialist training within special care dentistry. As part of my training I am completing a research degree. My research is focused on patients who have received allogenic stem cell transplants but who also received care from the special care dentistry department".

"You have agreed to participate in this study which involves an interview around the care you received from both the Haematology department and the Special Care Dentistry department. You are free to stop the interview at any point for a break and you can also withdraw from the study. Anything you say in the interview will remain confidential and will not affect the care you receive."

"The interview will be recorded however in the final write up only your initials and age will be used so you will remain anonymous. The study will form part of my research degree but the results will hopefully be disseminated in peer reviewed Haematology or dental journals".

"Have you got any questions about the study, at the moment?"

1. Tell me your story so far....
    a. diagnosis
    b. treatment to date
2. How did you feel when you found out you were being referred to the special care dentistry department?
    a. Were you aware of your referral?

Version 1 – 29/10/17

b. Do you think it's appropriate to have a care pathway with the dental hospital? – why?

c. What other specialities were you referred to?

d. How did these referrals make you feel?

3. What information did you receive about your referral to SCD?

    a. What information would you have like to have received prior to your referral to SCD?

4. Tell me about your previous experience of dental treatment?

    a. When did you last see a dentist prior to being assessed in SCD?

    b. Have you previously experienced dental treatment

        i. LA?

        ii. IVS?

        iii. GA?

5. What care did SCD provide you with?

    a. What advice did you receive about your teeth?

    b. How did that treatment make you feel?

    c. Do you know the reasons that treatment was provided?

    d. Is there anything else (dental-related) you would have liked prior to HSCT?

6. How did the dental treatment you received affect you through your HSCT?

    a. Did it affect your speech... function... appearance... why?

    b. What feeding regime did you have?

c. Did it affect your transplant at all… why?

d. What about the effect on your daily life??

7. What problems… if any… did you experience throughout your stay in hospital?

   a. Any pain? – soft tissues/teeth?

   b. Any problems cleaning your mouth?

   c. Why do you think you had these problems/ no problems?

8. Review of quantitative questionnaires – discussion around some of their responses…

9. Tell me about your feelings of dental treatment in the future?

   a. Who do you think should provide your dental treatment?

10. Finally… what advice would you give to patients embarking on the same care pathway as you?

    a. What improvements do you think we could make to our service?

    b. Would you want more advice… when… why?

7.18 Appendix 18: Transcription example

Gender: Male

Age: 34

Diagnosis: MDS

Date of interview: 23/10/18

Time of interview: 11.00

CWD: Ok... err good morning thank you for agreeing to speak to me errm as you know my name's Charlotte I'm doing a study, a project looking at the service that's provided between the errm the stem cell transplant department and the special care dentistry department...

P6: Ok

CWD: ...errm so it's a conversation there's a few questions erm you're free to stop at any point, your free to withdraw at any point, I'll destroy your material at that stage if that's what you want

P6: Ok

CWD:...are you happy with that?

P6: Yes

CWD: Ok, so the first question or the first thing I want to talk about is can you tell me your your journey so far from the point of view of the medical diagnosis and the treatment that you had?

P6: Errrrm... explain what I've gone through... is that the question?

CWD: Yeh what you've gone through, so yeh

P6: So, ok so errrm I had the transplant, so I had the chemo before the transplant is that what you... ok so I I had I got admitted errrm on the 6th of September, the 7th of September I had the sorry the 7th of September 2017 I had my line, my Hickman line installed, the 8th was errrm the 8th 9th 10th and 11th was radiotherapy, total body irradication errm twice a day, on the 11th I came back to the Royal and errrm on the 12th I had err I think 2 doses of chemotherapy and then the 13th I had errrm I think I had fluids and then I think the 14th I had the stem cell transplant. And then, no, 2 days,. the next day I after that I had the 2 doses of chemotherapy and then after that I had fluids again

CWD: Yeh

P6: Errrm and then I think around that time I started to have I started to lose my errrm taste errrm and I think actually it might have been a couple of days before that actually and me hair as well errm emotionally I think it was quite... quite depressing errm having no hair whilst being wheeled through the hospital and people starring at you errrm that was quite quite upsetting actually especially when everyone's looking at you err in that your feeling quite quite sick so for everybody to see

CWD: Ummm

P6: You in that state errm yeh it was quite, err that added on to the the experience I think so... I think if there was any improvement you could do there maybe maybe not let everybody see with, with half your hair sticking out (laughs), half of your hair out and obviously feeling sick, sick as a dog, so yeh so errm so err me hair eventually went, me taste buds must of went for maybe, I think a good month, good month or so errrm all I could taste was MacDonald's cheese that was the that was everything, everything tasted like MacDonald's cheese believe it or not so ummm very strange errrm err the

experience in the room itself wasn't that bad I had a lot of movies I'd prepared meself to be entertained throughout so I made sure I wasn't... just staring at the wall for instance for the 5 weeks I was there... errrm so I felt quite good in meself errm did everything the doctors and nurses said you know errrm... with the mouthwashes, brushing your teeth several times a day after each errrm meal errm lets have a think, and I used a electric shaver if I needed to shave, which I didn't eventually obviously coz the hair, the hair went but errm I think that's mostly it really around while I was admitted.

CWD: And what were you diagnosed with...

P6: Errrm I

CWD: ...why did you need the stem cell transplant?

P6: I had err MDS I think it's called myeloid dysplastic syndrome errrm which is where the red blood cells, you probably know that already but yeh MDS I had errm yeh

CWD: And at what point were you referred to the special care dentistry department?

P6: Err that was before my transplant, before I was admitted in the royal errm I think errm one of the doctors or consultants wanted to make sure I had the right toothpaste I think yourselves gave it gave me that toothpaste and make sure that me errrm you know there was no infections with me teeth or what not errrm yeh

CWD: So, the doctors made you aware that you were being referred?

P6: Yes, it was them yeh

CWD: And... do you... can you explain to me why you think that referral was made?

P6: ... Err.. I think that was made... just to just to check off another box in case that you know I I had the infection in my gum you know maybe I had a dodgy tooth for instance and could of easily got and infection in there once me immune system was down so that's what I assume is your just covering all the corners if that's what you mean.. yeh

CWD: And errm... how did being referred to a dentist, in the mists of everything, how did that make you feel?

P6: Errrrm it felt... quite good actually that I was having like a you know I was being well cared should I say yeh so felt like I was kind of special in a way you know that they didn't, they were covering all the angle that's what I'm trying to say yeh..

CWD: Ok.... and... what what did we what information erm sorry I can't even speak now, err I can't get my words out, erm what advice did you get from the special care department, what did we do for you when you came over?

P6: Errrm (cough), you evaluate my errrm oral hygiene erm you... err advised me this use the toothpaste you was gonna give me and to err how ever many times to use it each day and to keep it on keep the actual paste on your mouth don't rinse it at the end of the err you know brushing your mouth, brushing your teeth emmm errrm yeh

CWD: Did you need any treatment doing?

P6: No, no well we were going to do some some thing, but we were going to wait till after...

CWD: Ok

P6: ...which we did in the end...which was yeh just a filling

CWD: Fantastic and when did that filling happen, when did you come back to us afterwards?

P6: Errrm I came back... probably about a year after me transplant funnily enough yeh about a year I think it was maybe 10 months after

CWD: And do you think that was the right time to come back?

P6: No I should have came back a lot sooner but I don't know what happened, I don't know whether it was my fault not following it up with yourselves probably I think it was my fault for not phoning coz I think I had a we arranged err a filling I got an appointment letter in the post but I was having me transplant at that time so I couldn't make it, so we cancelled it and it never came back up so... so yeh

CWD: Ok and... so during your transplant so your time in hospital so you mentioned your taste...

P6: Yeh

CWD: ...went...

P6: ummhmm

CWD: ...so how long was it gone for, what sort, you said everything tasted like MacDonald's cheese...

P6: Yeh

CWD: ...but was there anything you could eat?

P6: Errrm I err yeh I ate for a good while there err first of all me taste did go for maybe a a good month maybe longer actually it's hard to remember exactly how long errm it slowly came back though err so yeh errrm I could eat quite a lot at the start of it all while my taste was gone but towards the end of err me being admitted or discharged sorry I err couldn't eat much... yeh...

CWD: And was... sorry

P6: It's alright, sorry... I was gonna tell you when this was...

CWD: And so, was your mouth sore as well? or...

P6: Errrm cough a little bit I had a few ulcers on me cheeks errm and me throat was a little bit sore...

CWD: Ok

P6: ... but no, I still manged to eat I think yeh it wasn't that bad

CWD: Did they provide you with a NG tube at any point?

P6: No

CWD: No? so you were eating all solid foods?

P6: Errrm they did try and give me that several times and I I said I said no but every time, I just tried to force down which I did yeh... it wasn't easy (laughs)

CWD: No... can I ask why you refused the tube?

P6: Errrm... it it's just something that I didn't like the the look of really it seemed quite uncomfortable errrm so yeh I was quite happy trying to force it down me

CWD: Yeh... erm... so did you have any problems cleaning your mouth when you were in hospital?

P6: Errrm... cough pain wise no... errm no I was probably, I took me time I got a baby brush a baby toothbrush I'm not sure if yourselves told me that or I think you did actually yeh... so it was I brushed quite gently as I say took my time and had no problems.

CWD: And were you seei still using the mouthwashes at that point?

P6: Err I was yeh, I used it throughout the stem cell transplant...

CWD: yeh

P6: ...5 weeks, it was 5 weeks 3 days

CWD: And the tooth... toothpaste?

P6: Err yes that's what I used, I can't remember the name of the toothpaste but it errm what it was sorry

CWD: It's ok, don't worry... and errm... so... before you had your stem cell transplant where did you get your dental treatment provided from?

P6: Err that was err I couldn't tell you off the top of my head the name of it but it's just round the corner from where I used to live errm

CWD: And how often did you go?

P6: Errrm I think it was every 6 months I think the appointment was it? Yeh it was every 6 months I used to get an appointment in the card, in the post...

CWD: Yeh

P6: ...yeh I think it was

CWD: So, you felt ok about dentists?

P6: Yeh yeh I mean no saying that I'm never I've never been comfortable with dentists err its needles I suppose it's not the best are they so no

CWD: Yeh

(laughs)

CWD: Em so having seen ourselves have your views on dental treatment changed at all?

P6: Errrm... I wouldn't say it's it's changed from yourselves, it's changed from my experience with the stem cell and the amount of needles that you go through having that experience, so I think coz I had a bit of a phobia before this with needles, I think that's maybe helped me going the dentist a bit more yeh

CWD: Yeh... and so you came back to us, were you happy that you came back to see us at that point rather than your normal dentist, after the transplant for a filling?

P6: Err yeh I was yeh

CWD: And why was that?

P6: Err well well it seems it's not that my regular dentist was unclean but I erm the NHS dentists seem to be you'd assume they're more hygienic errm that's what I think anyways, it's probably not but I get that impression that they are

CWD: Ok and going forwards to the future errm who do you think should be providing your dental care now?

P6: Errrm I'd say my my you know the one I used to go to before the treatment

CWD: ...and what makes you say that?

P6: Errrm when I was having the special care the dentist you know the special care in the dental hospital they said that I didn't no longer need to go there so, I was well enough to go to the yeh

CWD: Yeh fantastic, and with regards to your mouth and oral hygiene if you met someone about to start the stem cell process what advice would you give them?

P6: Hmmm what advice would I give them err I would say to get plenty of entertainment (laughs) take in a computer or you know laptop with games or videos or if they had films something to keep your mind busy. Errrm (sigh) errrm... (cough)... maybe.. no do everything, they the nurses and doctors tell you you know they do tell you to do as you know oral hygiene is a big thing and it certainly helped me with not having as many blisters and pain I suppose than other patients that were admitted at the same time. Errm.. what else I would say erm... hmmm there's not much else to be honest I think that's that's the main ones I think that was the biggest err help for me

CWD: Ok... and would you have wanted more advice from about your mouth about dentistry, well dental advice beforehand?

P6: Errrm... no I think you guys when I first seen you before the transplant I think errm I think you covered everything you explained what needed to be done. Errm errm and you gave me a bit of advice at the current state which was you know there was nothing

that was... any problems currently at the time, so I think no I think you gave me some nice peace of mind at the time yeh

CWD: And were you ok with the fact that we were going to do the filling afterwards?

P6: Yeh I mean, ok as could be as I say I'm not fond of dentists but errm no it was yeh I think I would have preferred it after, I can drag it out as long as possible (laughs)

CWD: Is there anything additional you want to add?

P6: Errrm about the stem cell transplant part I think if someone was there who errrm maybe some more advice prior to the transplant would have been better for peace of mind, obviously it's quite nervous for anybody to have such a erm such a treatment for something like that a transplant err I think any advice would have been great, something to settle the nerves so yeh... if someone was there who knew what it felt like maybe errm yeh that would have been good that would have been better...

CWD: Ok

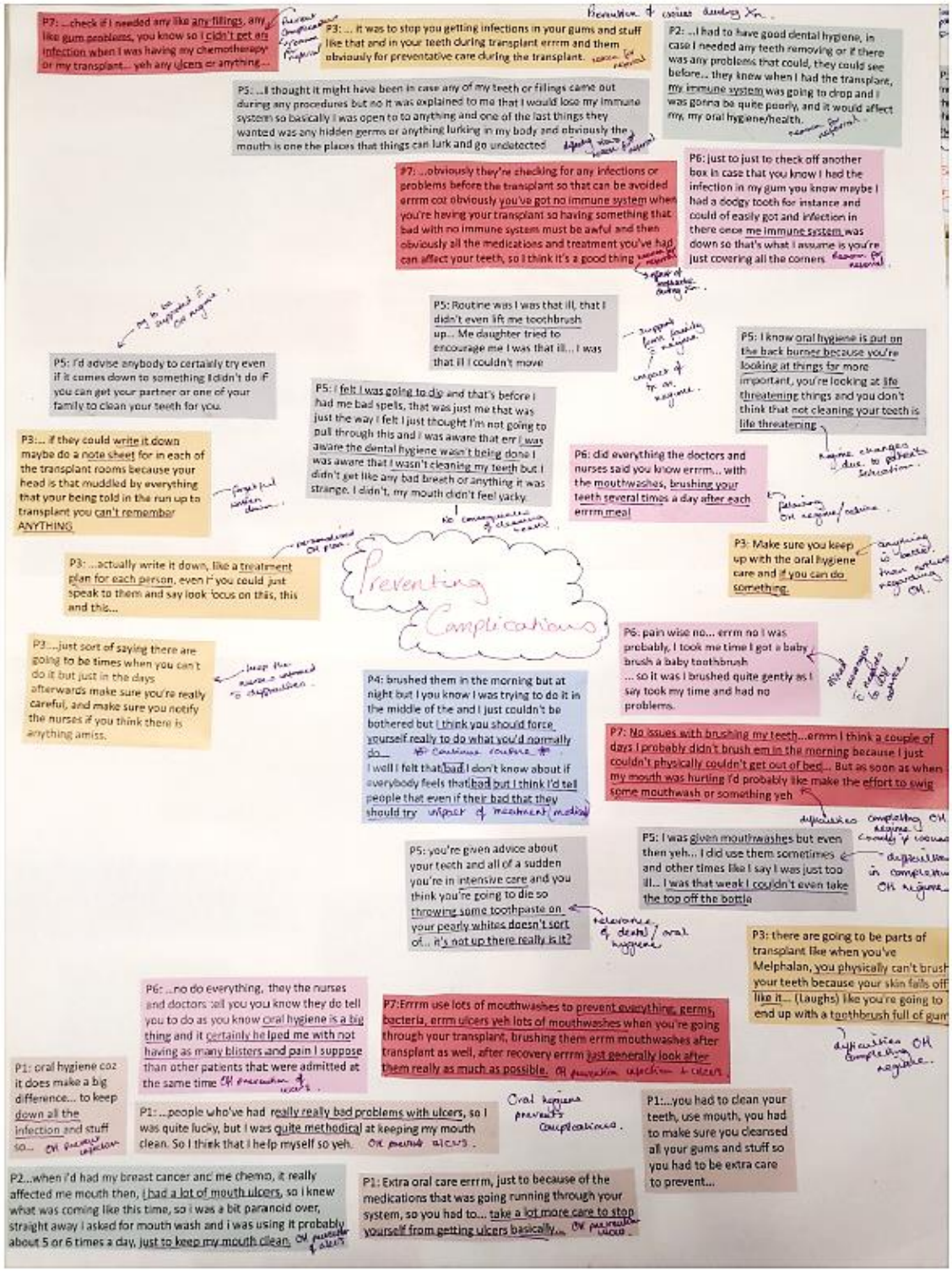
P6: ...that's it

CWD: Thank you, thank you

P6: You're welcome

7.19 Appendix 19: Data analysis process – Powerpoint® example

7.20 Appendix 20: Data analysis

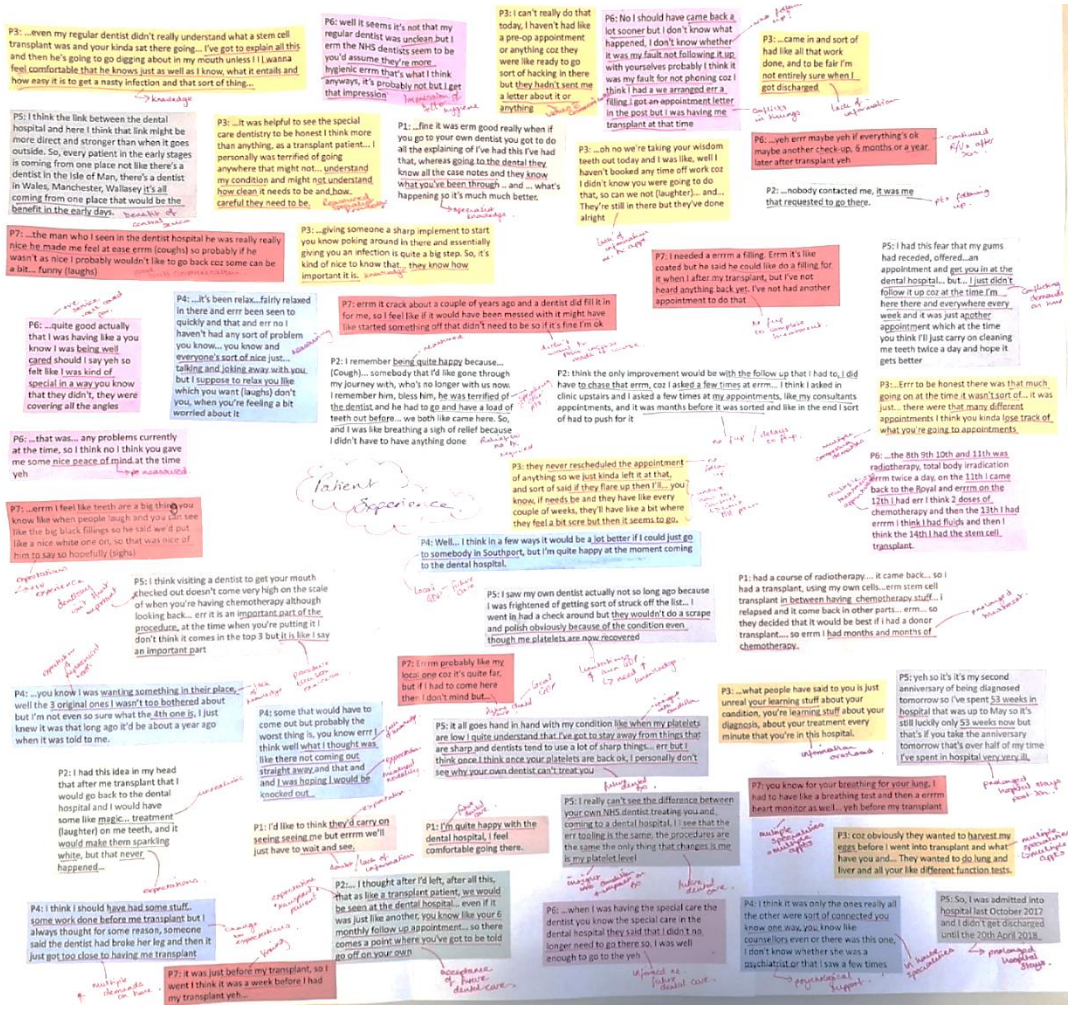


Theme	Categories	Codes	Quotes
Preventing transplant related complications	Dental referral	Dental prevention	P2: …I had to have good dental hygiene, in case I needed any teeth removing or if there was any problems that could, they could see before… P3: errrm and then obviously for preventative care during the transplant.
		Need for dental treatment	P2: in case I needed any teeth removing or if there was any problems that could, they could see before… P5: …I thought it might have been in case any of my teeth or fillings came out during any procedures… P7: … you know so I didn't get an infection when I was having my chemotherapy or my transplant… yeh any ulcers or anything…
		Lack of immune system/infections	P2: they knew when I had the transplant, my immune system was going to drop and I was gonna be quite poorly, and it would affect my, my oral hygiene/health P3: … it was to stop you getting infections in your gums and stuff like that and in your teeth during transplant P5: …but no it was explained to me that I would lose my immune system so basically I was open to to anything and one of the last things they wanted was any hidden germs or anything lurking in my body and obviously the mouth is one the places that things can lurk and go undetected P6: just to just to check off another box in case that you know I had the infection in my gum you know maybe I had a dodgy tooth for instance and could of easily got and infection in there once me immune system was down so that's what I assume is you're just covering all the corners P7: you know so I didn't get an infection when I was having my chemotherapy or my transplant… yeh any ulcers or anything… P7: …obviously they're checking for any infections or problems before the transplant so that can be avoided errrm coz obviously you've got no immune system when you're having your transplant so

			having something that bad with no immune system must be awful and then obviously all the medications and treatment you've had can affect your teeth, so I think it's a good thing
	Patient motivation regarding oral hygiene	Prevents complications	P1: …you had to clean your teeth, use mouth, you had to make sure you cleansed all your gums and stuff so you had to be extra care to prevent… P1: oral hygiene coz it does make a big difference… to keep down all the infection and stuff so… P1: …people who've had really really bad problems with ulcers, so I was quite lucky, but I was quite methodical at keeping my mouth clean. So I think that I help myself so yeh. P2…when i'd had my breast cancer and me chemo, it really affected me mouth then, i had a lot of mouth ulcers, so i knew what was coming like this time, so i was a bit paranoid over, straight away i asked for mouth wash and i was using it probably about 5 or 6 times a day, just to keep my mouth clean. P6: …no do everything, they the nurses and doctors tell you you know they do tell you to do as you know oral hygiene is a big thing and it certainly helped me with not having as many blisters and pain I suppose than other patients that were admitted at the same time P7:Errrm use lots of mouthwashes to prevent everything, germs, bacteria, errm ulcers yeh lots of mouthwashes when you're going through your transplant, brushing them errm mouthwashes after transplant as well, after recovery errrm just generally look after them really as much as possible.
		Oral hygiene regime	P3: Make sure you keep up with the oral hygiene care and if you can do something. P3: there are going to be parts of transplant like when you've Melphalan, you physically can't brush your teeth because your skin falls off like it… (Laughs) like you're going to end up with a toothbrush full of gum. P4: brushed them in the morning but at night but I you know I was trying to do it in the middle of the and I just couldn't be bothered but I think you should force yourself really to do what you'd normally do…

			I well I felt that bad I don't know about if everybody feels that bad but I think I'd tell people that even if their bad that they should try P5: Routine was I was that ill, that I didn't even lift me toothbrush up... Me daughter tried to encourage me I was that ill... I was that ill I couldn't move P5: I was given mouthwashes but even then yeh... I did use them sometimes and other times like I say I was just too ill... I was that weak I couldn't even take the top off the bottle P5: I know oral hygiene is put on the back burner because you're looking at things far more important, you're looking at life threatening things and you don't think that not cleaning your teeth is life threatening P5: I felt I was going to die and that's before I had me bad spells, that was just me that was just the way I felt I just thought I'm not going to pull through this and I was aware that err I was aware the dental hygiene wasn't being done I was aware that I wasn't cleaning my teeth but I didn't get like any bad breath or anything it was strange. I didn't, my mouth didn't feel yacky. P5: you're given advice about your teeth and all of a sudden you're in intensive care and you think you're going to die so throwing some toothpaste on your pearly whites doesn't sort of... it's not up there really is it? P6: did everything the doctors and nurses said you know errrm... with the mouthwashes, brushing your teeth several times a day after each errrm meal P6: pain wise no... errm no I was probably, I took me time I got a baby brush a baby toothbrush ... so it was I brushed quite gently as I say took my time and had no problems. P7: No issues with brushing my teeth...errrm I think a couple of days I probably didn't brush em in the morning because I just couldn't physically couldn't get out of bed... But as soon as when my mouth was hurting I'd probably like make the effort to swig some mouthwash or something yeh
		Future suggestions	P3:...just sort of saying there are going to be times when you can't do it but just in the days afterwards make sure you're really careful, and make sure you notify the nurses if you think there is anything amiss.

			P3: ...actually write it down, like a treatment plan for each person, even if you could just speak to them and say look focus on this, this and this... P3:... if they could write it down maybe do a note sheet for in each of the transplant rooms because your head is that muddled by everything that your being told in the run up to transplant you can't remember ANYTHING P5: I'd advise anybody to certainly try even if it comes down to something I didn't do if you can get your partner or one of your family to clean your teeth for you.

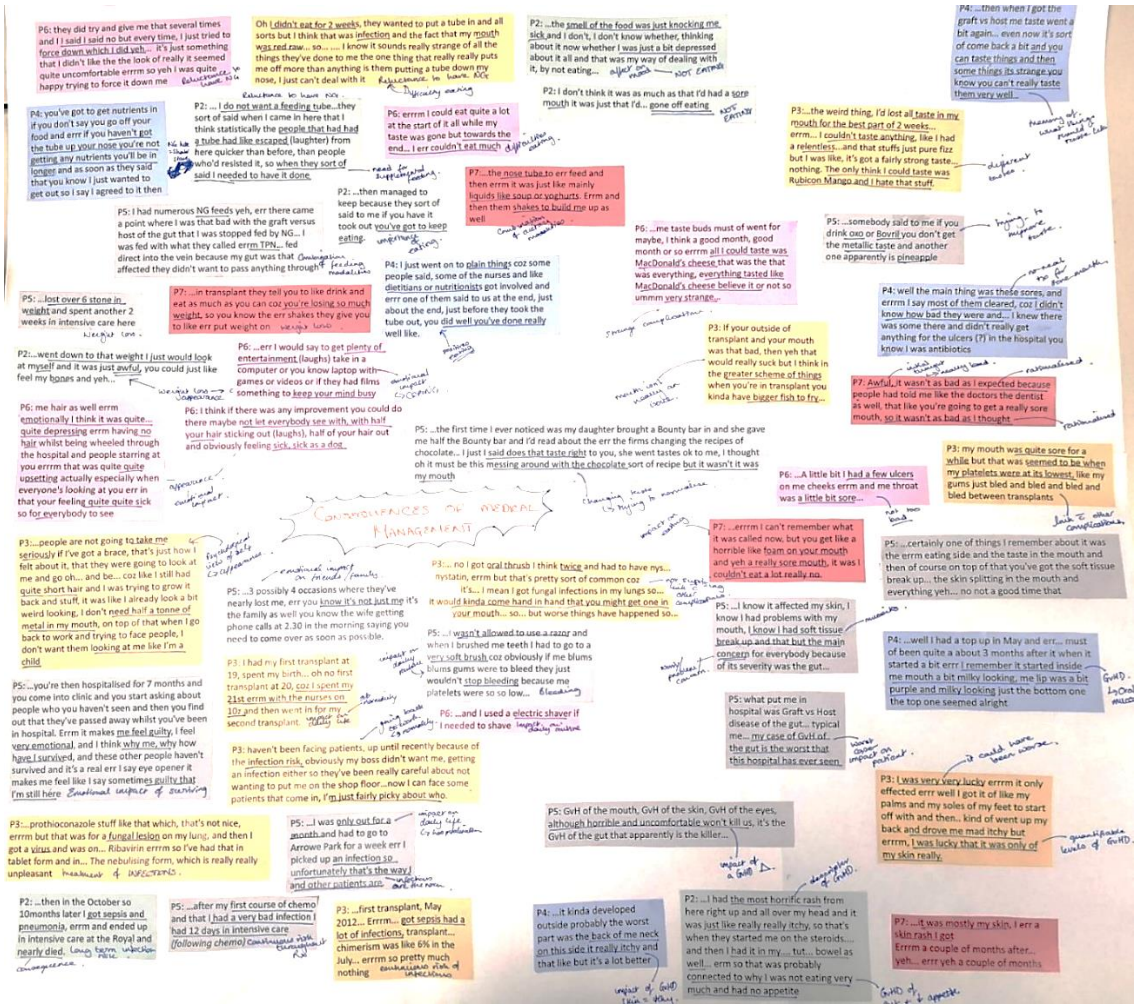

P3: ...even my regular dentist didn't really understand what a stem cell transplant was and your kinda sat there going... I've got to explain all this and then he's going to go digging about in my mouth unless I I wanna feel comfortable that he knows just as well as I know, what it entails and how easy it is to get a nasty infection and that sort of thing...
P6: well it seems it's not that my regular dentist was unclean but I erm the NHS dentists seem to be you'd assume they're more... hygienic errm that's what I think anyways, it's probably not but I get that impression
P3: I can't really do that today, I haven't had like a pre-op appointment or anything coz they were like ready to go sort of hacking in there but they hadn't sent me a letter about it or anything
P6: No I should have came back a lot sooner but I don't know what happened, I don't know whether it was my fault not following it up with yourselves probably I think it was my fault for not phoning coz I think I had a we arranged err a filling I got an appointment letter in the post but I was having me transplant at that time
P3: ...came in and sort of had like all that work done, and to be fair I'm not entirely sure when I got discharged
P5: I think the link between the dental hospital and here I think that link might be more direct and stronger than when it goes outside. So, every patient in the early stages is coming from one place not like there's a dentist in the Isle of Man, there's a dentist in Wales, Manchester, Wallasey it's all coming from one place that would be the benefit in the early days.
P3: ...it was helpful to see the special care dentistry to be honest I think more than anything, as a transplant patient... I personally was terrified of going anywhere that might not... understand my condition and might not understand how clean it needs to be and how, careful they need to be.
P1: ...fine it was erm good really when if you go to your own dentist you got to do all the explaining of I've had this I've had that, whereas going to the dental they know all the case notes and they know what you've been through .. and ... what's happening so it's much much better.
P3: ...oh no we're taking your wisdom teeth out today and I was like, well I haven't booked any time off work coz I didn't know you were going to do that, so can we not (laughter)... and... They're still in there but they've done alright
P6: ...yeh errr maybe yeh if everything's ok maybe another check-up, 6 months or a year later after transplant yeh
P2: ...nobody contacted me, it was me that requested to go there.
P7: ...the man who I seen in the dentist hospital he was really really nice he made me feel at ease errm (coughs) so probably if he wasn't as nice I probably wouldn't like to go back coz some can be a bit... funny (laughs)
P3: ...giving someone a sharp implement to start you know poking around in there and essentially giving you an infection is quite a big step. So, it's kind of nice to know that ... they know how important it is.
P7: I needed a errrm a filling. Errm it's like coated but he said he could like do a filling for it when I after my transplant, but I've not heard anything back yet. I've not had another appointment to do that
P5: I had this fear that my gums had receded, offered...an appointment and get you in at the dental hospital... but... I just didn't follow it up coz at the time I'm ... here there and everywhere every week and it was just another appointment which at the time you think I'll just carry on cleaning me teeth twice a day and hope it gets better
P6: ...quite good actually that I was having like a you know I was being well cared should I say yeh so felt like I was kind of special in a way you know that they didn't, they were covering all the angles
P4: ...it's been relax...fairly relaxed in there and errr been seen to quickly and that and err no I haven't had any sort of problem you know... you know and everyone's sort of nice just... talking and joking away with you but I suppose to relax you like which you want (laughs) don't you, when you're feeling a bit worried about it
P7: errm it crack about a couple of years ago and a dentist did fill it in for me, so I feel like if it would have been messed with it might have like started something off that didn't need to be so if it's fine I'm ok
P2: I remember being quite happy because... (Cough)... somebody that I'd like gone through my journey with, who's no longer with us now. I remember him, bless him, he was terrified of the dentist and he had to go and have a load of teeth out before... we both like came here. So, and I was like breathing a sigh of relief because I didn't have to have anything done
P2: think the only improvement would be with the follow up that I had to, I did have to chase that errm, coz I asked a few times at errm... I think I asked in clinic upstairs and I asked a few times at my appointments, like my consultants appointments, and it was months before it was sorted and like in the end I sort of had to push for it
P3:...Errr to be honest there was that much going on at the time it wasn't sort of... it was just... there were that many different appointments I think you kinda lose track of what you're going to appointments
P6: ...that was... any problems currently at the time, so I think no I think you gave me some nice peace of mind at the time yeh
Patient Experience
P3: they never rescheduled the appointment of anything so we just kinda left it at that, and sort of said if they flare up then I'll... you know, if needs be and they have like every couple of weeks, they'll have like a bit where they feel a bit sore but then it seems to go.
P6: ...the 8th 9th 10th and 11th was radiotherapy, total body irradiation errm twice a day, on the 11th I came back to the Royal and errrm on the 12th I had err I think 2 doses of chemotherapy and then the 13th I had errrm I think I had fluids and then I think the 14th I had the stem cell transplant.
P7: ...errm I feel like teeth are a big thing you know like when people laugh and you can see like the big black fillings so he said we'd put like a nice white one on, so that was nice of him to say so hopefully (sighs)
P4: Well... I think in a few ways it would be a lot better if I could just go to somebody in Southport, but I'm quite happy at the moment coming to the dental hospital.
P5: I think visiting a dentist to get your mouth checked out doesn't come very high on the scale of when you're having chemotherapy although looking back... err it is an important part of the procedure, at the time when you're putting it I don't think it comes in the top 3 but it is like I say an important part
P5: I saw my own dentist actually not so long ago because I was frightened of getting sort of struck off the list... I went in had a check around but they wouldn't do a scrape and polish obviously because of the condition even though me platelets are now recovered
P1: had a course of radiotherapy.... it came back... so I had a transplant, using my own cells...erm stem cell transplant in between having chemotherapy stuff... I relapsed and it come back in other parts... erm... so they decided that it would be best if I had a donor transplant.... so errm I had months and months of chemotherapy.
P7: Errm probably like my local one coz it's quite far, but if I had to come here then I don't mind but...
P4: ...you know I was wanting something in their place, well the 3 original ones I wasn't too bothered about but I'm not even so sure what the 4th one is, I just knew it was that long ago it'd be about a year ago when it was told to me.
P4: some that would have to come out but probably the worst thing is, you know errr I think well what I thought was like there not coming out straight away and that and and I was hoping I would be knocked out...
P5: it all goes hand in hand with my condition like when my platelets are low I quite understand that I've got to stay away from things that are sharp and dentists tend to use a lot of sharp things... err but I think once I think once your platelets are back ok, I personally don't see why your own dentist can't treat you
P3: ...what people have said to you is just unreal your learning stuff about your condition, you're learning stuff about your diagnosis, about your treatment every minute that you're in this hospital.
P5: yeh so it's it's my second anniversary of being diagnosed tomorrow so I've spent 53 weeks in hospital that was up to May so it's still luckily only 53 weeks now but that's if you take the anniversary tomorrow that's over half of my time I've spent in hospital very very ill.
P2: I had this idea in my head that after me transplant that I would go back to the dental hospital and I would have some like magic... treatment (laughter) on me teeth, and it would make them sparkling white, but that never happened...
P1: I'd like to think they'd carry on seeing seeing me but errrm we'll just have to wait and see.
P1: I'm quite happy with the dental hospital, I feel comfortable going there.
P5: I really can't see the difference between your own NHS dentist treating you and coming to a dental hospital, I see that the err tooling is the same, the procedures are the same the only thing that changes is me is my platelet level
P7: you know for your breathing for your lung, I had to have like a breathing test and then a errrm heart monitor as well... yeh before my transplant
P4: I think I should have had some stuff, some work done before me transplant but I always thought for some reason, someone said the dentist had broke her leg and then it just got too close to having me transplant
P2:... I thought after I'd left, after all this, that as like a transplant patient, we would be seen at the dental hospital... even if it was just like another, you know like your 6 monthly follow up appointment... so there comes a point where you've got to be told go off on your own
P6: ...when I was having the special care the dentist you know the special care in the dental hospital they said that I didn't no longer need to go there so, I was well enough to go to the yeh
P4: I think it was only the ones really all the other were sort of connected you know one way, you know like counsellors even or there was this one, I don't know whether she was a psychiatrist or that I saw a few times
P3: coz obviously they wanted to harvest my eggs before I went into transplant and what have you and... They wanted to do lung and liver and all your like different function tests.
P5: So, I was admitted into hospital last October 2017 and I didn't get discharged until the 20th April 2018.
P7: it was just before my transplant, so I went I think it was a week before I had my transplant yeh...

Theme	Categories	Codes	Quotes
	Beliefs around dental management	Specialist knowledge	P1: ...fine it was erm good really when if you go to your own dentist you got to do all the explaining of I've had this I've had that, whereas going to the dental they know all the case notes and they know what you've been through .. and ... what's happening so it's much much better. P3: ...It was helpful to see the special care dentistry to be honest I think more than anything, as a transplant patient... I personally was terrified of going anywhere that might not... understand my condition and might not understand how clean it needs to be and how careful they need to be. P3: ...even my regular dentist didn't really understand what a stem cell transplant was and your kinda sat there going... I've got to explain all this and then he's going to go digging about in my mouth unless I I I wanna feel comfortable that he knows just as well as I know, what it entails and how easy it is to get a nasty infection and that sort of thing... P3: ...giving someone a sharp implement to start you know poking around in there and essentially giving you an infection is quite a big step. So, it's kind of nice to know that... they know how important it is.
		Reassurance	P2: I remember being quite happy because... (Cough)... somebody that I'd like gone through my journey with, who's no longer with us now. I remember him, bless him, he was terrified of the dentist and he had to go and have a load of teeth out before... we both like came here. So, and I was like breathing a sigh of relief because I didn't have to have anything done P4: ...it's been relax...fairly relaxed in there and errr been seen to quickly and that and err no I haven't had any sort of problem you know... you know and everyone's sort of nice just... talking and joking away with you but I suppose to relax you like which you want (laughs) don't you, when you're feeling a bit worried about it P5: I think the link between the dental hospital and here I think that link might be more direct and stronger than when it goes outside. So, every patient in the early stages is coming from one place not like there's a dentist in the Isle of Man, there's a dentist in Wales, Manchester, Wallasey it's all coming from one place that would be the benefit in the early days.
			P6: ...quite good actually that I was having like a you know I was being well cared should I say yeh so felt like I was kind of special in a way you know that they didn't, they were covering all the angles P6: ...that was... any problems currently at the time, so I think no I think you gave me some nice peace of mind at the time yeh P7: ...the man who I seen in the dentist hospital he was really really nice he made me feel at ease errm (coughs) so probably if he wasn't as nice I probably wouldn't like to go back coz some can be a bit... funny (laughs)
		Treatment provided	P2: I had this idea in my head that after me transplant that I would go back to the dental hospital and I would have some like magic... treatment (laughter) on me teeth, and it would make them sparkling white, but that never happened... P4: ...you know I was wanting something in their place, well the 3 original ones I wasn't too bothered about but I'm not even so sure what the 4th one is, I just knew it was that long ago it'd be about a year ago when it was told to me. P4: some that would have to come out but probably the worst thing is, you know errr I think well what I thought was like there not coming out straight away and that and and I was hoping I would be knocked out P5: I think visiting a dentist to get your mouth checked out doesn't come very high on the scale of when you're having chemotherapy although looking back... err it is an important part of the procedure, at the time when you're putting it I don't think it comes in the top 3 but it is like I say an important part P7: ...errm I feel like teeth are a big thing you know like when people laugh and you can see like the big black fillings so he said we'd put like a nice white one on, so that was nice of him to say so hopefully (sighs)
		Future dental treatment	P1: I'm quite happy with the dental hospital, I feel comfortable going there. P1: I'd like to think they'd carry on seeing seeing me but errrm we'll just have to wait and see.

			P2:... I thought after I'd left, after all this, that as like a transplant patient, we would be seen at the dental hospital... even if it was just like another, you know like your 6 monthly follow up appointment... so there comes a point where you've got to be told go off on your own P4: Well... I think in a few ways it would be a lot better if I could just go to somebody in Southport, but I'm quite happy at the moment coming to the dental hospital. P5: I saw my own dentist actually not so long ago because I was frightened of getting sort of struck off the list... I went in had a check around but they wouldn't do a scrape and polish obviously because of the condition even though me platelets are now recovered P5: it all goes hand in hand with my condition like when my platelets are low I quite understand that I've got to stay away from things that are sharp and dentists tend to use a lot of sharp things... err but I think once I think once your platelets are back ok, I personally don't see why your own dentist can't treat you P5: I really can't see the difference between your own NHS dentist treating you and coming to a dental hospital, I I see that the err tooling is the same, the procedures are the same the only thing that changes is me is my platelet level P6: ...when I was having the special care the dentist you know the special care in the dental hospital they said that I didn't no longer need to go there so, I was well enough to go to the yeh P7: Errrm probably like my local one coz it's quite far, but if I had to come here then I don't mind but...
	Competing demands and expectations	Numerous appointments	P1: had a course of radiotherapy.... it came back... so i had a transplant, using my own cells...erm stem cell transplant in between having chemotherapy stuff... i relapsed and it come back in other parts... erm... so they decided that it would be best if i had a donor transplant.... so errm I had months and months of chemotherapy P3:...Errr to be honest there was that much going on at the time it wasn't sort of... it was just... there were that many different appointments I think you kinda lose track of what you're going to appointments

			P3: ...what people have said to you is just unreal your learning stuff about your condition, you're learning stuff about your diagnosis, about your treatment every minute that you're in this hospital. P3: coz obviously they wanted to harvest my eggs before I went into transplant and what have you and... They wanted to do lung and liver and all your like different function tests. P4: I think I should have had some stuff.. some work done before me transplant but I always thought for some reason, someone said the dentist had broke her leg and then it just got too close to having me transplant P4: I think it was only the ones really all the other were sort of connected you know one way, you know like counsellors even or there was this one, I don't know whether she was a psychiatrist or that I saw a few times P5: yeh so it's it's my second anniversary of being diagnosed tomorrow so I've spent 53 weeks in hospital that was up to May so it's still luckily only 53 weeks now but that's if you take the anniversary tomorrow that's over half of my time I've spent in hospital very very ill. P5: So, I was admitted into hospital last October 2017 and I didn't get discharged until the 20th April 2018 P6: ...the 8th 9th 10th and 11th was radiotherapy, total body irradication errm twice a day, on the 11th I came back to the Royal and errrm on the 12th I had err I think 2 doses of chemotherapy and then the 13th I had errrm I think I had fluids and then I think the 14th I had the stem cell transplant. P7: it was just before my transplant, so I went I think it was a week before I had my transplant yeh... P7: you know for your breathing for your lung, I had to have like a breathing test and then a errrm heart monitor as well... yeh before my transplant

		Follow up	P2: ...nobody contacted me, it was me that requested to go there. P7: ...yeh errr maybe yeh if everything's ok maybe another check-up, 6 months or a year later after transplant yeh P2: think the only improvement would be with the follow up that I had to, I did have to chase that errm, coz I asked a few times at errm... I think I asked in clinic upstairs and I asked a few times at my appointments, like my consultants appointments, and it was months before it was sorted and like in the end I sort of had to push for it P3: they never rescheduled the appointment of anything so we just kinda left it at that, and sort of said if they flare up then I'll... you know, if needs be and they have like every couple of weeks, they'll have like a bit where they feel a bit sore but then it seems to go. P3: ...came in and sort of had like all that work done, and to be fair I'm not entirely sure when I got discharged P3: ...oh no we're taking your wisdom teeth out today and I was like, well I haven't booked any time off work coz I didn't know you were going to do that, so can we not (laughter)... and... They're still in there but they've done alright P3: I can't really do that today, I haven't had like a pre-op appointment or anything coz they were like ready to go sort of hacking in there but they hadn't sent me a letter about it or anything P6: No I should have came back a lot sooner but I don't know what happened, I don't know whether it was my fault not following it up with yourselves probably I think it was my fault for not phoning coz I think I had a we arranged err a filling I got an appointment letter in the post but I was having me transplant at that time P7: I needed a errrm a filling. Errm it's like coated but he said he could like do a filling for it when I after my transplant, but I've not heard anything back yet. I've not had another appointment to do that


P6: they did try and give me that several times and I I said I said no but every time, I just tried to force down which I did yeh... it's just something that I didn't like the the look of really it seemed quite uncomfortable errrm so yeh I was quite happy trying to force it down me
Oh I didn't eat for 2 weeks, they wanted to put a tube in and all sorts but I think that was infection and the fact that my mouth was red raw... so... ... I know it sounds really strange of all the things they've done to me the one thing that really really puts me off more than anything is them putting a tube down my nose, I just can't deal with it
P2: ...the smell of the food was just knocking me sick and I don't, I don't know whether, thinking about it now whether I was just a bit depressed about it all and that was my way of dealing with it, by not eating...
P4: ...then when I got the graft vs host me taste went a bit again... even now it's sort of come back a bit and you can taste things and then some things its strange you know you can't really taste them very well ...
P6: you've got to get nutrients in if you don't say you go off your food and errr if you haven't got the tube up your nose you're not getting any nutrients you'll be in longer and as soon as they said that you know I just wanted to get out so I say I agreed to it then
P2: ... I do not want a feeding tube...they sort of said when I came in here that I think statistically the people that had had a tube had like escaped (laughter) from here quicker than before, than people who'd resisted it, so when they sort of said I needed to have it done
P6: errrm I could eat quite a lot at the start of it all while my taste was gone but towards the end... I err couldn't eat much
P2: I don't think it was as much as that I'd had a sore mouth it was just that I'd... gone off eating
P3:...the weird thing, I'd lost all taste in my mouth for the best part of 2 weeks ... errrm... I couldn't taste anything, like I had a relentless...and that stuffs just pure fizz but I was like, it's got a fairly strong taste... nothing. The only think I could taste was Rubicon Mango and I hate that stuff
P7:...the nose tube to err feed and then errm it was just like mainly liquids like soup or yoghurts. Errm and then them shakes to build me up as well
P2: ...then managed to keep because they sort of said to me if you have it took out you've got to keep eating.
P5: I had numerous NG feeds yeh, err there came a point where I was that bad with the graft versus host of the gut that I was stopped fed by NG... I was fed with what they called errm TPN... fed direct into the vein because my gut was that affected they didn't want to pass anything through
P6: ...me taste buds must of went for maybe, I think a good month, good month or so errrm all I could taste was MacDonald's cheese that was the that was everything, everything tasted like MacDonald's cheese believe it or not so ummm very strange...
P5:...somebody said to me if you drink oxo or Bovril you don't get the metallic taste and another one apparently is pineapple
P4: I just went on to plain things coz some people said, some of the nurses and like dietitians or nutritionists got involved and err one of them said to us at the end, just about the end, just before they took the tube out, you did well you've done really well like.
P4: well the main thing was these sores, and errrm I say most of them cleared, coz I didn't know how bad they were and.... I knew there was some there and didn't really get anything for the ulcers (?) in the hospital you know. I was antibiotics
P5: ...lost over 6 stone in weight and spent another 2 weeks in intensive care here
P7: ...in transplant they tell you to like drink and eat as much as you can coz you're losing so much weight, so you know the err shakes they give you to like err put weight on
P3: If your outside of transplant and your mouth was that bad, then yeh that would really suck but I think in the greater scheme of things when you're in transplant you kinda have bigger fish to fry...
P7: Awful, it wasn't as bad as I expected because people had told me like the doctors the dentist as well, that like you're going to get a really sore mouth, so it wasn't as bad as I thought
P2:...went down to that weight I just would look at myself and it was just awful, you could just like feel my bones and yeh...
P6: ...err I would say to get plenty of entertainment (laughs) take in a computer or you know laptop with games or videos or if they had films or something to keep your mind busy
P6: me hair as well errm emotionally I think it was quite... quite depressing errm having no hair whilst being wheeled through the hospital and people starring at you errrm that was quite quite upsetting actually especially when everyone's looking at you err in that your feeling quite quite sick so for everybody to see
P6: I think if there was any improvement you could do there maybe not let everybody see with, with half your hair sticking out (laughs), half of your hair out and obviously feeling sick, sick as a dog
P5: ...the first time I ever noticed was my daughter brought a Bounty bar in and she gave me half the Bounty bar and I'd read about the err the firms changing the recipes of chocolate... I just I said does that taste right to you, she went tastes ok to me, I thought oh it must be this messing around with the chocolate sort of recipe but it wasn't it was my mouth
CONSEQUENCES OF MEDICAL MANAGEMENT
P6: ...A little bit I had a few ulcers on me cheeks errm and me throat was a little bit sore...
P3: my mouth was quite sore for a while but that was seemed to be when my platelets were at its lowest, like my gums just bled and bled and bled and bled between transplants
P7: ...errrm I can't remember what it was called now, but you get like a horrible like foam on your mouth and yeh a really sore mouth, it was I couldn't eat a lot really no.
P5:...certainly one of things I remember about it was the errm eating side and the taste in the mouth and then of course on top of that you've got the soft tissue break up... the skin splitting in the mouth and everything yeh.... no not a good time that
P3:...people are not going to take me seriously if I've got a brace, that's just how I felt about it, that they were going to look at me and go oh... and be... coz like I still had quite short hair and I was trying to grow it back and stuff, it was like I already look a bit weird looking, I don't need half a tonne of metal in my mouth, on top of that when I go back to work and trying to face people, I don't want them looking at me like I'm a child
P5: ...3 possibly 4 occasions where they've nearly lost me, err you know it's not just me it's the family as well you know the wife getting phone calls at 2.30 in the morning saying you need to come over as soon as possible.
P3:... no I got oral thrush I think twice and had to have nys... nystatin, errm but that's pretty sort of common coz it's... I mean I got fungal infections in my lungs so... it would kinda come hand in hand that you might get one in your mouth... so... but worse things have happened so...
P5: ...I know it affected my skin, I know I had problems with my mouth, I know I had soft tissue break up and that but the main concern for everybody because of its severity was the gut...
P4: ...well I had a top up in May and err... must of been quite a about 3 months after it when it started a bit errr I remember it started inside me mouth a bit milky looking, me lip was a bit purple and milky looking just the bottom one the top one seemed alright
P5:...you're then hospitalised for 7 months and you come into clinic and you start asking about people who you haven't seen and then you find out that they've passed away whilst you've been in hospital. Errm it makes me feel guilty, I feel very emotional, and I think why me, why how have I survived, and these other people haven't survived and it's a real err I say eye opener it makes me feel like I say sometimes guilty that I'm still here
P3: I had my first transplant at 19, spent my birth... oh no first transplant at 20, coz I spent my 21st errm with the nurses on 10r and then went in for my second transplant.
P5: ...I wasn't allowed to use a razor and when I brushed me teeth I had to go to a very soft brush coz obviously if me blums blums gums were to bleed they just wouldn't stop bleeding because me platelets were so so low...
P6: ...and I used a electric shaver if I needed to shave
P3: haven't been facing patients, up until recently because of the infection risk, obviously my boss didn't want me, getting an infection either so they've been really careful about not wanting to put me on the shop floor...now I can face some patients that come in, I'm just fairly picky about who.
P5: what put me in hospital was Graft vs Host disease of the gut... typical me... my case of GvH of the gut is the worst that this hospital has ever seen
P3:...prothioconazole stuff like that which, that's not nice, errrm but that was for a fungal lesion on my lung, and then I got a virus and was on... Ribavirin errrm so I've had that in tablet form and in... The nebulising form, which is really really unpleasant
P5: ...I was only out for a month and had to go to Arrowe Park for a week err I picked up an infection so... unfortunately that's the way I and other patients are
P5: GvH of the mouth, GvH of the skin, GvH of the eyes, although horrible and uncomfortable won't kill us, it's the GvH of the gut that apparently is the killer...
P3: I was very very lucky errrm it only effected errr well I got it of like my palms and my soles of my feet to start off with and then.. kind of went up my back and drove me mad itchy but errrm, I was lucky that it was only of my skin really.
P2: ...then in the October so 10months later I got sepsis and pneumonia, errm and ended up in intensive care at the Royal and nearly died.
P5: ...after my first course of chemo and that I had a very bad infection I had 12 days in intensive care (following chemo)
P3: ...first transplant, May 2012... Errrm... got sepsis had a lot of infections, transplant... chimerism was like 6% in the July... errrm so pretty much nothing
P4: ...it kinda developed outside probably the worst part was the back of me neck on this side it really itchy and that like but it's a lot better
P2: ...I had the most horrific rash from here right up and all over my head and it was just like really really itchy, so that's when they started me on the steroids.... and then I had it in my.... tut... bowel as well... errm so that was probably connected to why I was not eating very much and had no appetite
P7: ...it was mostly my skin, I err a skin rash I got Errrm a couple of months after... yeh... errr yeh a couple of months

Theme	Categories	Codes	Quotes
Consequences of medical management	Medical complications	Infections	P2: ...then in the October so 10months later I got sepsis and pneumonia, errm and ended up in intensive care at the Royal and nearly died. P3: ...first transplant, May 2012... Errrm... got sepsis had a lot of infections, transplant... chimerism was like 6% in the July... errrm so pretty much nothing P3:...prothioconazole stuff like that which, that's not nice, errrm but that was for a fungal lesion on my lung, and then I got a virus and was on... Ribavirin errrm so I've had that in tablet form and in... The nebulising form, which is really really unpleasant P5: ...after my first course of chemo and that I had a very bad infection I had 12 days in intensive care *(following chemo)* P5: ...I was only out for a month and had to go to Arrowe Park for a week err I picked up an infection so unfortunately that's the way I and other patients are.
		GvHD	P2: ...I had the most horrific rash from here right up and all over my head and it was just like really really itchy, so that's when they started me on the steroids.... and then I had it in my.... tut... bowel as well... erm so that was probably connected to why I was not eating very much and had no appetite P3: I was very very lucky errrm it only effected errr well I got it of like my palms and my soles of my feet to start off with and then.. kind of went up my back and drove me mad itchy but errrm, I was lucky that it was only of my skin really. P4: ...it kinda developed outside probably the worst part was the back of me neck on this side it really itchy and that like but it's a lot better P4: ...well I had a top up in May and err... must of been quite a about 3 months after it when it started a bit errr I remember it started inside me mouth a bit milky looking, me lip was a bit purple and milky looking just the bottom one the top one seemed alright

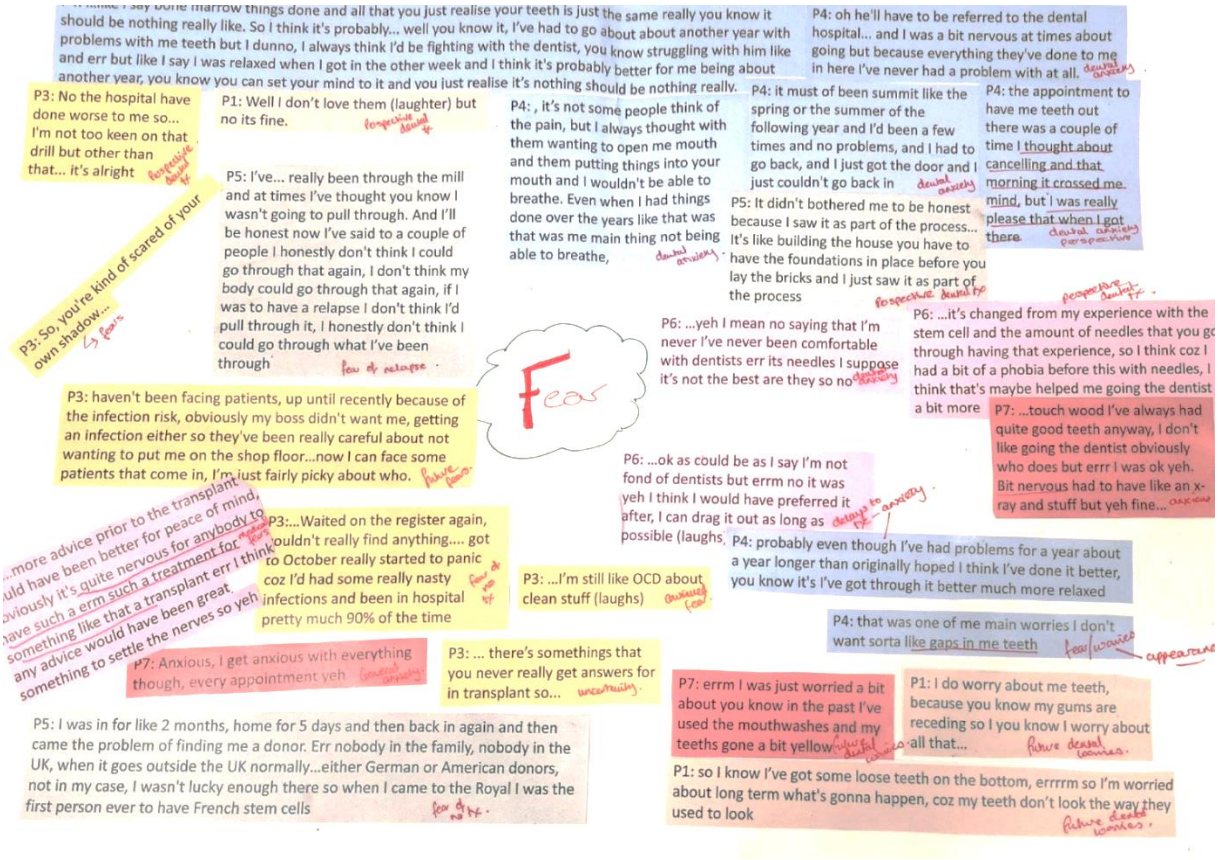
			P5: what put me in hospital was Graft vs Host disease of the gut... typical me... my case of GvH of the gut is the worst that this hospital has ever seen P5: ...I know it affected my skin, I know I had problems with my mouth, I know I had soft tissue break up and that but the main concern for everybody because of its severity was the gut... P5: GvH of the mouth, GvH of the skin, GvH of the eyes, although horrible and uncomfortable won't kill us, it's the GvH of the gut that apparently is the killer... P7: ...it was mostly my skin, I err a skin rash I got... Errrm a couple of months after... yeh... errr yeh a couple of months
		Diet/nutrition	P2: I don't think it was as much as that I'd had a sore mouth it was just that I'd... gone off eating P2: ...the smell of the food was just knocking me sick and I don't, I don't know whether, thinking about it now whether I was just a bit depressed about it all and that was my way of dealing with it, by not eating... P2: ... I do not want a feeding tube...they sort of said when I came in here that I think statistically the people that had had a tube had like escaped (laughter) from here quicker than before, than people who'd resisted it, so when they sort of said I needed to have it done P2: ...then managed to keep because they sort of said to me if you have it took out you've got to keep eating. P3: Oh I didn't eat for 2 weeks, they wanted to put a tube in and all sorts but I think that was infection and the fact that my mouth was red raw... so... .... I know it sounds really strange of all the things they've done to me the one thing that really really puts me off more than anything is them putting a tube down my nose, I just can't deal with it P4: you've got to get nutrients in if you don't say you go off your food and errr if you haven't got the tube up your nose you're not getting any nutrients you'll be in longer and as soon as they said that you know I just wanted to get out so I say I agreed to it then

			P4: I just went on to plain things coz some people said, some of the nurses and like dietitians or nutritionists got involved and errr one of them said to us at the end, just about the end, just before they took the tube out, you did well you've done really well like. P5: I had numerous NG feeds yeh, err there came a point where I was that bad with the graft versus host of the gut that I was stopped fed by NG... I was fed with what they called errm TPN... fed direct into the vein because my gut was that affected they didn't want to pass anything through P6: they did try and give me that several times and I I said I said no but every time, I just tried to force down which I did yeh... it's just something that I didn't like the the look of really it seemed quite uncomfortable errrm so yeh I was quite happy trying to force it down me P6: errrm I could eat quite a lot at the start of it all while my taste was gone but towards the end... I err couldn't eat much P7: ...in transplant they tell you to like drink and eat as much as you can coz you're losing so much weight, so you know the err shakes they give you to like err put weight on P7:...the nose tube to err feed and then errm it was just like mainly liquids like soup or yoghurts. Errm and then them shakes to build me up as well
	Oral complications	Realistic insight	P3: If your outside of transplant and your mouth was that bad, then yeh that would really suck but I think in the greater scheme of things when you're in transplant you kinda have bigger fish to fry... P7: Awful, it wasn't as bad as I expected because people had told me like the doctors the dentist as well, that like you're going to get a really sore mouth, so it wasn't as bad as I thought
		Dysguesia	P3:...the weird thing, I'd lost all taste in my mouth for the best part of 2 weeks... errm... I couldn't taste anything, like I had a relentless...and that stuffs just pure fizz but I was like, it's got a fairly strong taste... nothing. The only think I could taste was Rubicon Mango and I hate that stuff. P4: ...then when I got the graft vs host me taste went a bit again... even now it's sort of come back a bit and you can taste things and then some things its strange you know you can't really taste them very well

			P5: ...the first time I ever noticed was my daughter brought a Bounty bar in and she gave me half the Bounty bar and I'd read about the err the firms changing the recipes of chocolate... I just I said does that taste right to you, she went tastes ok to me, I thought oh it must be this messing around with the chocolate sort of recipe but it wasn't it was my mouth P5: ...certainly one of things I remember about it was the errm eating side and the taste in the mouth P5: ...somebody said to me if you drink oxo or Bovril you don't get the metallic taste and another one apparently is pineapple P6: ...me taste buds must of went for maybe, I think a good month, good month or so errrm all I could taste was MacDonald's cheese that was the that was everything, everything tasted like MacDonald's cheese believe it or not so ummm very strange...
		Mucositis	P3: my mouth was quite sore for a while but that was seemed to be when my platelets were at its lowest, like my gums just bled and bled and bled and bled between transplants P4: well the main thing was these sores, and errrm I say most of them cleared, coz I didn't know how bad they were and... I knew there was some there and didn't really get anything for the ulcers (?) in the hospital you know I was antibiotics P5: ...then of course on top of that you've got the soft tissue break up... the skin splitting in the mouth and everything yeh... no not a good time that P6: ...A little bit I had a few ulcers on me cheeks errm and me throat was a little bit sore... P7: ...errrm I can't remember what it was called now, but you get like a horrible like foam on your mouth and yeh a really sore mouth, it was I couldn't eat a lot really no.
		Candida	P3:... no I got oral thrush I think twice and had to have nys... nystatin, errm but that's pretty sort of common coz it's... I mean I got fungal infections in my lungs so... it would kinda come hand in hand that you might get one in your mouth... so... but worse things have happened so...

	Impact on normal routine	Emotional impact	P5: ...you're then hospitalised for 7 months and you come into clinic and you start asking about people who you haven't seen and then you find out that they've passed away whilst you've been in hospital. Errm it makes me feel guilty, I feel very emotional, and I think why me, why how have I survived, and these other people haven't survived and it's a real err I say eye opener it makes me feel like I say sometimes guilty that I'm still here P5: ...3 possibly 4 occasions where they've nearly lost me, err you know it's not just me it's the family as well you know the wife getting phone calls at 2.30 in the morning saying you need to come over as soon as possible.
		Appearance	P2:...went down to that weight I just would look at myself and it was just awful, you could just like feel my bones and yeh... P3:...people are not going to take me seriously if I've got a brace, that's just how I felt about it, that they were going to look at me and go oh... and be... coz like I still had quite short hair and I was trying to grow it back and stuff, it was like I already look a bit weird looking, I don't need half a tonne of metal in my mouth, on top of that when I go back to work and trying to face people, I don't want them looking at me like I'm a child P5: ...lost over 6 stone in weight and spent another 2 weeks in intensive care here P6: me hair as well errm emotionally I think it was quite... quite depressing errm having no hair whilst being wheeled through the hospital and people starring at you errrm that was quite quite upsetting actually especially when everyone's looking at you err in that your feeling quite quite sick so for everybody to see P6: I think if there was any improvement you could do there maybe not let everybody see with, with half your hair sticking out (laughs), half of your hair out and obviously feeling sick, sick as a dog
		Routine	P3: haven't been facing patients, up until recently because of the infection risk, obviously my boss didn't want me, getting an infection either so they've been really careful about not wanting to put me on the shop floor...now I can face some patients that come in, I'm just fairly picky about who.

			P5: ...I wasn't allowed to use a razor and when I brushed me teeth I had to go to a very soft brush coz obviously if me blums blums gums were to bleed they just wouldn't stop bleeding because me platelets were so so low... P6: ...and I used a electric shaver if I needed to shave



Theme	Categories	Codes	Quote
Psychological impact of treatment	Medical fears	Fear of no treatment	P3:...Waited on the register again, couldn't really find anything.... got to October really started to panic coz I'd had some really nasty infections and been in hospital pretty much 90% of the time P5: I was in for like 2 months, home for 5 days and then back in again and then came the problem of finding me a donor. Err nobody in the family, nobody in the UK, when it goes outside the UK normally...either German or American donors, not in my case, I wasn't lucky enough there so when I came to the Royal I was the first person ever to have French stem cells
		Generalised anxiety	P3: So, you're kind of scared of your own shadow... P3: ...I'm still like OCD about clean stuff (laughs) P6: ...more advice prior to the transplant would have been better for peace of mind, obviously it's quite nervous for anybody to have such a erm such a treatment for something like that a transplant err I think any advice would have been great, something to settle the nerves so yeh P7: Anxious, I get anxious with everything though, every appointment yeh

		Fear of treatment failing	P1: ...i been on lots of different chemotherapies, coz each one from the beginning of this didn't work... wasn't making any difference. P2:...then I was told that I had no option other than the stem cell transplant, otherwise.... I wouldn't get better. P3: ... there's somethings that you never really get answers for in transplant so... P5: I've... really been through the mill and at times I've thought you know I wasn't going to pull through. And I'll be honest now I've said to a couple of people I honestly don't think I could go through that again, I don't think my body could go through that again, if I was to have a relapse I don't think I'd pull through it, I honestly don't think I could go through what I've been through P7: when I was in remission for about a year and a half, then it comeback and I relapsed in June 2017 which then meant that I had to have a bone marrow errrm transplant
	Dental fears	Dental anxiety	P4: oh he'll have to be referred to the dental hospital... and I was a bit nervous at times about going but because everything they've done to me in here I've never had a problem with at all. P4: Like from 2006, I just never went the dentist, and I knew things were getting more, were getting worse, there was times where I said about forcing myself to go P4: it must of been summit like the spring or the summer of the following year and I'd been a few times and no problems, and I had to go back, and I just got the door and I just couldn't go back in

			P4: , it's not some people think of the pain, but I always thought with them wanting to open me mouth and them putting things into your mouth and I wouldn't be able to breathe. Even when I had things done over the years like that was that was me main thing not being able to breathe, P4: the appointment to have me teeth out there was a couple of time I thought about cancelling and that morning it crossed me mind, but I was really please that when I got there P4: probably even though I've had problems for a year about a year longer than originally hoped I think I've done it better, you know it's I've got through it better much more relaxed P6: ...yeh I mean no saying that I'm never I've never been comfortable with dentists err its needles I suppose it's not the best are they so no P6: ...ok as could be as I say I'm not fond of dentists but errm no it was yeh I think I would have preferred it after, I can drag it out as long as possible (laughs) P7: ...touch wood I've always had quite good teeth anyway, I don't like going the dentist obviously who does but errr I was ok yeh. Bit nervous had to have like an x-ray and stuff but yeh fine...
		Perspective	P1: Well I don't love them (laughter) but no its fine. P3: No the hospital have done worse to me so... I'm not too keen on that drill but other than that... it's alright P4: ...like I say bone marrow things done and all that you just realise your teeth is just the same really you know it should be nothing really like. So I think it's probably... well

			you know it, I've had to go about about another year with problems with me teeth but I dunno, I always think I'd be fighting with the dentist, you know struggling with him like and err but like I say I was relaxed when I got in the other week and I think it's probably better for me being about another year, you know you can set your mind to it and you just realise it's nothing should be nothing really. P5: It didn't bothered me to be honest because I saw it as part of the process... It's like building the house you have to have the foundations in place before you lay the bricks and I just saw it as part of the process P6: ...it's changed from my experience with the stem cell and the amount of needles that you go through having that experience, so I think coz I had a bit of a phobia before this with needles, I think that's maybe helped me going the dentist a bit more
		Future dental concerns	P1: so I know I've got some loose teeth on the bottom, errrrm so I'm worried about long term what's gonna happen, coz my teeth don't look the way they used to look P1: I do worry about me teeth, because you know my gums are receding so I you know I worry about all that... P4: that was one of me main worries I don't want sorta like gaps in me teeth P7: errm I was just worried a bit about you know in the past I've used the mouthwashes and my teeths gone a bit yellow