



# The prevalence and configuration of nausea in patients receiving intravenous chemotherapy in a private oncology centre in South Africa

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## **PREFACE**

The researcher is aware of the difference in the title and the content of the dissertation regarding 'prevalence' and 'incidence'. This is a technical error and did not impact the methodology of the study. The study maintained an approach to the research as laid out in the aims and objectives throughout for the duration of the projects, with 'incidence' as concept. The title will be rectified by submitting it to the Human Research Ethics Committee for approval.

## DEDICATION

I dedicate this dissertation to every person who gave up their precious time  
to grant me the opportunity to complete this dissertation.

## **ACKNOWLEDGEMENTS**

I have received generous help from many quarters during the completion of this dissertation, people whom I would like to acknowledge here with deep gratitude:

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## **ABSTRACT**

The development of effective antiemetic treatment has contributed to the relieving of chemotherapy-induced vomiting in chemotherapy patients. There is, however, a growing concern that chemotherapy-induced nausea and vomiting (CINV) research focuses primarily on vomiting, while nausea is perceived to be of secondary importance. All patients receiving antiemetic prophylaxis with intravenous chemotherapy do not have complete control of nausea. This study focused on chemotherapy-induced nausea, collecting information on the true incidence and patterns thereof. Valuable information was gained through having a project focusing particularly on nausea, contributing to a better understanding of this distressing and debilitating adverse event of chemotherapy.

This prospective, observational study included all patients receiving intravenous chemotherapy at a private oncology clinic in South Africa. One hundred subjects were enrolled over an eight-month period in 2017. This broad inclusion of patients gave a review of 'real-life' experiences of patients. The study used patient diaries with visual analogue scales (VAS) and patient-reported outcome measures (PROMs) to get data to resemble patients' experience as accurately as possible, in order to ensure data compatibility. Patients were issued with standard antiemetic prophylactic therapy according to CINV guidelines and the patients' demographics were summarised using descriptive statistics. The prevalence of nausea was compared with the prevalence of vomiting in the overall phase. Possible patient related risk factors were documented, including age, gender, previous CINV, the capacity of the current chemotherapy to induce CINV (emetogenicity), history of motion sickness, history of morning sickness and alcohol use in the previous two years.

Not much published literature exists on the incidence of chemotherapy-induced nausea. Most literature focuses on CINV as one entity. Despite decades of research, the mechanism of CINV or nausea (not related the chemotherapy) is still not clearly understood. There is, however, very clear data on the negative impact of nausea on the quality of life of patients receiving chemotherapy. The patient characteristics contributing to an increased risk of experiencing nausea are also well documented in the literature. This study reflected the published data on risk factors, in particular female gender, a history of motion sickness, a history of morning sickness, age below 60 years and chemotherapy with high and moderate emetogenicity, placing the patient at higher risk of experiencing nausea.

Enrolled patients had to complete diaries on their experience of nausea and vomiting for the first three consecutive cycles of their treatment. After cycle one, 95 evaluable diaries were collected

and cycle two and three delivered 87 and 79 evaluable diaries, respectively. The group received a variety of intravenous chemotherapy regimens with emetogenicity, including 26% low emetogenic chemotherapy patients, 24% moderately emetogenic chemotherapy patients and 46% high emetogenic chemotherapy patients. Despite all patients receiving guideline consistent CINV prophylaxis, 57.9% of all patients experienced nausea, compared to only 24.2% vomiting during cycle one. The mean time to first event of nausea was 28.5 hours after chemotherapy infusion, with a VAS mean intensity of 5.88 out of ten. For patients experiencing intermittent nausea, the mean duration per episode of nausea experienced was 4.07 hours but 31.6% patients experienced continuous nausea. These findings were reflected during all three cycles of treatment.

Of the patients experiencing nausea during cycle one, 94.7% of them also experienced anticipatory nausea the day before commencing treatment with cycle two, and 93.3% before commencing cycle three ( $p = 0.000$ ). No vomiting incidents were recorded by 61.8% of patients during cycle one who experienced nausea, and 72.7% and 61.1% during cycle two and three. Risk factors that were found to have a significant negative impact on nausea was female gender, age below 60 years and higher emetogenicity of chemotherapy treatment.

Chemotherapy-induced nausea is a persisting adverse event of patients diagnosed with cancer, independent from chemotherapy-induced vomiting. Patients with risk factors have an increased potential to experience chemotherapy-induced nausea, as well as experiencing nausea refractory to Guideline Consistent CINV Prophylaxis (GCCP) and rescue medication. These patients need to be approached differently in the clinic in regard to managing nausea. Precise following of GCCP and rescue medication must go hand in hand with patient education on the management of chemotherapy-induced nausea, to empower the patient in managing their nausea with the prescribed medication. There is a need for more studies with nausea as primary endpoint, and updated CINV guidelines that distinguish between prophylaxis and treatment of nausea, and that of vomiting.

## LIST OF ABBREVIATIONS

5-HT <sub>3</sub>	Serotonin receptor
AC	Anthracycline/cyclophosphamide combination chemotherapy treatment
ACTH	Adrenocorticotrophic hormone
ADH	Antidiuretic hormone (vasopressin)
ANOVA	Analysis of variance
APF530	An injectable subcutaneous long-acting formulation of granisetron, not yet registered for use in South Africa
ASCO	American Society of Clinical Oncology
BCRP	Breast cancer resistance protein
CINV	Chemotherapy-induced nausea and vomiting
CNS	Central nervous system
Cytochrome P450	Enzymes responsible for the metabolism of a large number of drugs in the liver and gastrointestinal tract (the 'P' refers to the pink compound formed when combined with carbon monoxide, and '450' to the absorption peak of 450nm on a spectrophotometer). Two of the main enzymes in the cytochrome P450 group are CYP3A4 and CYP2A6 (Pharmacology, 1999:80)
CYP2A6	See cytochrome P450
CYP3A4	See cytochrome P450
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FLIE	Functional Living Index – Emesis
FU	Follow up.
GCCP	Guideline consistent CINV prophylaxis

GCP	Good Clinical Practice
HEC	High emetogenic chemotherapy
HRQoL	Health-related quality of life
LEC	Low emetogenic chemotherapy
MASCC	Multinational Association of Supportive Care in Cancer
MAT	MASCC Antiemetic Tool
MCC	Medicines Control Council (now SAHPRA)
MEC	Moderately emetogenic chemotherapy
MUSA	Medicine Usage in South Africa
NEPA	Netupitant/palonosetron combination
NCCN	National Comprehensive Cancer Network
NK-1	Neurokinin-1
NP1	New patient (first visit)
NP2	New patient (second visit)
NWU	North-West University
NTS	Nucleus tractus solitarius
PROM	Patient-reported outcome measure
SAHPRA	South African Health Products Regulatory Authority
SAOC	South African Oncology Consortium
SASMO	South African Society of Medical Oncologists
SPSS	Statistical package for the social science
VAS	Visual analogue scales

## LIST OF DEFENITIONS

Abdominal vagus nerve	The vagus nerve is the tenth (and longest) cranial nerve, composed of 20% efferent fibres and 80% sensory fibres. Its most important function is transmitting sensory information throughout the body (Howland, 2006:11). The abdominal vagus nerve is the branch of the parasympathetic vagus nerve carrying fibres to the abdominal viscera (Rang <i>et al.</i> , 1999:97).
Acute phase CINV	Acute chemotherapy-induced nausea and vomiting is typically defined as occurring within 24 hours (day one) post chemotherapy infusion (Aapro <i>et al.</i> , 2012:233; Moradian & Howell, 2015:217)
Afferent fibres	Fibres carrying information from the body to the brain, also called sensory fibres (Howland, 2006:12). Vagal afferent fibres connect the gastrointestinal tract to the brain and play a large role in the generation of nausea and vomiting (Andrews & Horn, 2006:109).
Anonymity	The identity of research participants is unknown, even to the study investigators (Brink <i>et al.</i> , 2012:208).
Area postrema	A region in the medulla involved in the vomiting reflex (Rang <i>et al.</i> , 1999:168). The area postrema is located in the floor of the fourth ventricle, containing the chemo trigger zone (Bashashati and McCallum, 2014:80).
Anticipatory nausea	A conditioned response occurring because of prior poor control of CINV in previous chemotherapy treatments (Burke <i>et al.</i> , 2011:132).
Breakthrough CINV	Nausea and/or vomiting despite standard antiemetic treatment during acute or delayed phase of treatment (Navari, 2015).
Delayed phase CINV	Chemotherapy-induced nausea and vomiting occurs 25-120 hours (day two – day five) post initiation of

	chemotherapy infusion (Hesketh, 2008:2482).
Chemoreceptor	A sensory nerve cell activated by chemical stimuli (Mosby's dictionary, 1994:308).
Chemoreceptor trigger zone	The area in the brain containing the reflex mechanism of vomiting (Rang <i>et al.</i> , 1999:377). It is located in the area postrema, in the floor of the fourth ventricle. The chemoreceptor trigger zone is outside the blood brain barrier and is sensitive to chemicals in the cerebrospinal fluid and blood, making it an important mediator in the emesis process (Bashashati & McCallum, 2014:80).
Central pattern generator	A key site in the brain, mediating vomiting. The central pattern generator coordinates prodromal activities, e.g. salivation and sweating (Bashashati and McCallum, 2014:80).
Conditioned flavour avoidance	A learned flavour aversion to foods or flavours associated with toxicosis, displayed by many species including humans. It is used in laboratories to study malaise in animals, particularly the rat. It is likely that a learned flavour aversion is an indicator of malaise or nausea, and this type of learning might serve to predict foods that should be avoided. A similar process may occur in patients diagnosed with cancer because they often show learned avoidance to foods and environmental stimuli accosted with chemotherapy treatment (Andrews & Horn, 2006:103-106).
Confidentiality	The identity of the research participants is known only to the study investigator(s) (Brink <i>et al.</i> , 2012:209).
Cycles of treatment	The schedule of chemotherapy given in repeated dosing intervals. This is issued in sync with the tumour cells' growth cycles for optimal therapeutic effect (Chabner & Longo, 2015:58).

Cytochrome P450	Enzymes responsible for the metabolism of a large number of drugs in the liver and gastrointestinal tract (the 'P' refers to the pink compound formed when combined with carbon monoxide, and '450' to the absorption peak of 450nm on a spectrophotometer). Two of the main enzymes in the cytochrome P450 group are CYP3A4 and CYP2A6 (Rang <i>et al.</i> , 1999:80)
Differential diagnosis	Distinguishing between two or more diseases with similar symptoms by systematically comparing their signs and symptoms (Baid, 2006:1007).
Dyspepsia	Symptoms localised in the epigastric region, including epigastric pain, fullness, burning sensation, nausea, belching and bloating (Ahmad <i>et al.</i> , 2018).
ECOG performance status	Eastern Cooperative Oncology Group – describes a patient's level of functioning in terms of their ability to care for themselves, daily activity and physical ability like walking and working (Sorensen, 1993:773).
Endocrine system	A network of glands that secrete hormones directly into the bloodstream, affecting the function of specific target organs (Mosby's Medical Dictionary, 1994:548). The endocrine system is a control system of ductless glands that secrete hormones within specific organs. The hormones act as messengers and are carried by the bloodstream to different cells in the body, which interpret these messages and act on them (Johnstone <i>et al.</i> , 2014:42).
Equipotent	Having equal effects or capacities (Merriam Webster's Dictionary, 2016)
Efferent fibres	Fibres sending signals from the brain to the body (Howland, 2006:12).
Emesis	See vomiting.

Functional Living Index Emesis (FLIE)	– A validated nausea- and vomiting-specific, patient-reported outcome instrument, measuring the effect of CINV on daily activities of patients' lives (Aapro <i>et al.</i> , 2006:1442).
Kaolin	See pica.
Medulla	The most internal part of the brain containing the cardiac, vasomotor and respiratory centres of the brain (Mosby's Dictionary, 1994:970).
Nausea	Unpleasant wavelike sensation that makes a patient feel sick and queasy. It can be accompanied by perspiration, tachycardia, excessive salivation and swallowing (Andrews & Sanger, 2014:108; Pleuvry, 2015:462). Pallor or flushing and a sensation of being cold or hot may be associated with the feeling of nausea (Garrett <i>et al.</i> , 2003:32).
Neurotransmitters	The network of chemical signals and associated receptors by which cells in the body communicate with one another (Rang <i>et al.</i> , 1999:94).
Nucleus tractus solitarius	Bundles of nerves located in the midbrain, processing information received from the body. The NTS plays a leading role in the creating, perceiving and reacting to the feeling of nausea (Hesketh, 2008:2484; Lang & Marvig, 1989:92).
Overall phase	The overall phase includes the acute phase and delayed phase of CINV (Moradian & Howell, 2015:217).
Parasympathetic nerves	Nerves outside the influence of voluntary control, e.g. contraction and relaxation of smooth muscle (Rang <i>et al.</i> , 1999:96).
Patient-reported outcome measure	Any report coming directly from a patient about a health condition and its treatment (Howell <i>et al.</i> , 2013:76).

Pica	The consumption of dirt or clay (a non-nutritive substance) following the ingestion of toxins commonly observed in animals and humans. This is also referred to as Kaolin ingestion (Andrews & Horn, 2006:106).
Real-world research	A form of evaluation. It examines personal experience and tries to understand the lived-in reality of the study subjects. This contrasts with the more controlled conditions of research done in a laboratory (Moran-Ellis, 1994). Real-world research is done to corroborate data obtained from earlier published clinical trials with a real-world community setting in practice (Hatoum <i>et al.</i> , 2012:946). In a real-world study, assessments are conducted within the context of usual practice (Gillmore <i>et al.</i> , 2014:72).
Refractory CINV	Nausea and vomiting that is unresponsive to treatment (Aapro <i>et al.</i> , 2012:233).
Reliability	The extent to which a measuring instrument is consistent in giving the same findings when used at different times (Creswell <i>et al.</i> , 2016:238).
Rescue medication	Medication issued to relieve breakthrough nausea and/or vomiting (Hesketh, 2008:2482).
Retching	A non-productive attempt to vomit (Gillmore <i>et al.</i> , 2014:69). Spasmodic contractions of the diaphragm and the muscles of the thorax and abdominal wall, with no gastric contents being expelled (Pleuvry, 2015:462). Also known as dry heaves (Garrett <i>et al.</i> , 2003:32).
Standard Guideline-based antiemetic regimen	Antiemetic prophylaxis recommended by guidelines in patients submitted to chemotherapy and radiotherapy. The guidelines are updated regularly by professional organisations according to the latest scientifically based findings in this field (Roila <i>et al.</i> , 2010:232).
Validity	The degree of credibility or accuracy of something

(Creswell *et al.*, 2016:74).

Vasopressin

A hormone that is important mainly for its actions on the kidney, also known as the antidiuretic hormone. Vasopressin plays a crucial role in the control of water in the body (Rang *et al.*, 1999: 287,415).

Vection

Vection enables the studying of nausea in healthy volunteers (Andrews & Sanger, 2014:5). It is the illusion of self-motion by using stimulus like moving visual fields to induce motion sickness in experiments (Balaban & Yates, 2017:11).

Visual Analog Scale (VAS)

A one hundred-millimetre (100 mm) line on which a mark is made to denote perceived nausea, where 0 mm represents 'no nausea' and 100 mm 'worst possible nausea' (Kenward *et al.*, 2015:38).

Vomiting

The expulsion of gastrointestinal contents from the mouth (Navari, 2014:180). Vomiting is characterised by contraction of the abdominal muscles, descent of the diaphragm, and opening of the gastric cardia, resulting in forceful expulsion of stomach contents from the mouth (Garrett *et al.*, 2003:32; Wood *et al.*, 2011).

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Chapter 2: Literature Review  
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Chapter 4: Conclusion, recommendations and limitations*

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**PROOF OF LANGUAGE EDITING**

## AUTHOR CONTRIBUTIONS

The contribution of each author of the study, entitled “The prevalence and configuration of nausea in patients receiving intravenous chemotherapy in a private oncology centre in South Africa”; the manuscript, entitled “The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy”, and poster presentation, entitled “Measuring nausea, an underestimated clinical reality in patients receiving intravenous chemotherapy” are stipulated in the following table:

Author	Contribution to the study
Ms T Smit	<ul style="list-style-type: none"> <li>• Planning and designing of the study project and research presented in the manuscript.</li> <li>• Writing of literature review.</li> <li>• Planning of statistical analysis plan.</li> <li>• Interpretation of results.</li> <li>• Planning, writing and compilation of the poster presentation.</li> <li>• Writing the final mini-dissertation and manuscript.</li> </ul>
Dr JM du Plessis (Supervisor)	<ul style="list-style-type: none"> <li>• Supervision of concept and design of the study and manuscript.</li> <li>• Supervision in writing of literature review and manuscript.</li> <li>• Reviewing of the manuscript and poster presentation for academic content and approval of version to be published.</li> </ul>
Ms I Kotze (Co-supervisor)	<ul style="list-style-type: none"> <li>• Supervision of the concept and design of the study and manuscript.</li> <li>• Supervision in the writing of the literature review and manuscript.</li> <li>• Reviewing of the manuscript and poster presentation for academic content and approval of the version to be published.</li> </ul>
Mrs M Cockeran	<ul style="list-style-type: none"> <li>• Statistical analysis of data.</li> <li>• Verification of the research design.</li> </ul>
Dr Erika Fourie	<ul style="list-style-type: none"> <li>• Guidance in the interpretation of the results.</li> </ul>



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15 April 2019

**Re: Thesis, Mrs T Smit, student number: 10775927**

We hereby confirm that the Statistical Consultation Services of the North-West University analysed the data of the above-mentioned student and assisted with the interpretation of the results. However, any opinion, findings or recommendations contained in this document are those of the author, and the Statistical Consultation Services of the NWU (Potchefstroom Campus) do not accept responsibility for the statistical correctness of the data reported.

Kind regards

A handwritten signature in black ink that reads 'E Fourie'.

**Dr E Fourie**

Senior Consultant: Statistical Consultation Services

The co-authors confirmed their different roles in this study, manuscript and oral presentation, as well as their permission that the manuscript may form part of the dissertation in the following statement:

*I declare that I have approved the above-mentioned manuscript and poster presentation and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the Master of Pharmacy degree in Pharmacy practice of Ms Teresa Smit.*



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Dr JM du Plessis



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Ms I Kotze



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Ms M Cockeran



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Ms T Smit

# CHAPTER 1 RESEARCH PROTOCOL

## 1.1 Introduction

Nausea and vomiting used to be one of the most feared adverse events of cytotoxic chemotherapy for cancer (referred to as chemotherapy in this document) (Feyer & Jordan, 2011:30). Due to evidence-based research and appropriately used antiemetic regimens, vomiting can be prevented in the majority of patients (Jordan *et al.*, 2014:197). Nausea, however, is still not clearly understood and is a great, unmet medical need for patients diagnosed with cancer (Feyer & Jordan, 2011:30; Jordan *et al.*, 2015:1081). Despite guideline-based antiemetic prophylaxis, 55-60% of patients still experience nausea, and its burden is often underestimated by the healthcare professionals (Grunberg *et al.*, 2004:2261; Sommariva *et al.*, 2016:13).

Nausea is an unpleasant sensation causing the desire to vomit. It is associated with physiological changes that involve a number of neurotransmitters and receptors (Andrews & Sanger, 2014:108). Chemotherapy-induced nausea and vomiting (CINV) presents in three phases. The acute phase occurs within 0-24 hours, post-start of chemotherapy infusion, whereas the delayed phase occurs within 25-120 hours, post-start of chemotherapy infusion (Moradian & Howell, 2015:217). Anticipatory CINV is triggered in patients by taste, odour, sight, and thoughts of anxiety due to a history of inadequate antiemetic prophylaxis in previous cycles; and occurs before subsequent chemotherapy cycles (Jordan *et al.*, 2014:197).

In clinical practice, patients typically receive multiple cycles of chemotherapy. Incidence of CINV increases with number of cycles received (Herrstedt *et al.*, 2011:1433). If CINV is not managed in the delayed phase, protection against acute CINV can be impaired as well. In addition, anticipatory nausea could develop, adding to the physiological, emotional and economic burden of treatment (Rapoport *et al.*, 2016:23).

Delayed nausea in particular, is more difficult to manage than nausea in the acute phase (Cohen *et al.*, 2007:497). The managing of delayed nausea is complicated by the fact that it occurs after the patient has left the clinic and is not available for direct observation. This has an impact on the patient's daily activities and quality of life. As a consequence, it can affect the outcome of the overall treatment due to premature termination of treatment by patients. Additionally, unmanaged nausea increases the economic burden of medical costs (Feyer & Jordan, 2011:30; Grunberg *et al.*, 2004:2261; Moradian & Howell, 2015:216).

Until recently, vomiting and retching have been the initial focus of antiemetic research and nausea was perceived to be of secondary importance (Andrews & Sanger, 2014:108; Rapoport *et al.*, 2015).

## 1.2 Background to study

Chemotherapeutic agents are classified into four different levels of emetogenicity (high, moderate, low or minimal). Guidelines for prevention and treatment of CINV are based on this classification and consist of combinations of dexamethasone, 5-hydroxytryptamine (serotonin) (5-HT<sub>3</sub>) receptor antagonists and neurokinin-1 (NK-1) receptor antagonists (Roila *et al.*, 2010:232; Rapoport *et al.*, 2015).

Since the 1990s, 5-HT<sub>3</sub> receptor antagonists are the most widely used antiemetic for managing acute phase CINV (Hesketh, 2008:2482). Corticosteroids are a cornerstone in combination therapy for CINV prophylaxis in the acute and delayed phases of CINV (Grunberg, 2007:233). The first NK-1 receptor antagonist was approved in 2003 and has brought significant relief in acute and delayed phase CINV (Schmoll *et al.*, 2006:1000). Several studies have shown effective CINV prophylactic activity with olanzapine, an antipsychotic agent (Navari, 2014:180).

The development of these effective antiemetic treatments has contributed to the resolution of the feared side effect of CINV in chemotherapy patients over the years. However, there is a growing concern that this presumed resolution only reflects the focus on vomiting (Andrews & Sanger, 2014:108). Healthcare professionals seem to underestimate the incidence and impact of nausea in chemotherapy patients. This is specifically true for the delayed phase, which occurs only after patients have left the clinic (Gilmore *et al.*, 2014:68; Grunberg *et al.*, 2013:1).

## 1.3 Problem statement

The treatment of nausea is an unmet medical need in patients receiving emetogenic chemotherapy for the treatment of cancer.

For many years, CINV has been regarded a single entity (Pirri *et al.*, 2013:375). Regardless of all the advances in research, the gaps around CINV stand. Newer reasoning being that nausea and vomiting are two discrete occurrences, with nausea not being well-addressed (Grunberg *et al.*, 2013:1). Not all patients receiving antiemetic prophylaxis with intravenous chemotherapy have complete control of nausea (Basch *et al.*, 2011:4189).

Despite of substantial improvements in the control of vomiting and the availability of new agents, the control of nausea is still a major unmet medical need in patients diagnosed with cancer (Navari, 2013:249). Nausea has an impact on the patient's quality of life, as well as the outcome and financial cost of their treatment (Sommariva *et al.*, 2016:13).

Chemotherapy-induced nausea is not life-threatening but has a vast impact on the patient and their treatment. Nausea leads to anorexia, malnutrition, dehydration and anxiety towards chemotherapy (Abe *et al.*, 2015). Patients who experience nausea are often discouraged to complete planned treatment, as it has a negative impact on their quality of life and daily activities (Aapro *et al.*, 2012:1986). This collectively plays a role in the overall recovery period of the patient. The need of additional rescue medication, emergency treatment and loss in employment productivity adds to the economic burden of medical care (Bashashati & McCallum, 2014:79; Gilmore *et al.*, 2014:68; Nolte *et al.*, 1998:771).

Valuable information will be gained through having a study focusing particularly on nausea. It will contribute to a better understanding of this distressing and debilitating adverse event of chemotherapy. This prospective, observational study will collect data on the pattern of CINV, focusing on nausea in particular. The use of collected data from a patient-reported outcome measure (PROM), will give a more accurate reflection of the real-life symptoms experienced by the patients (Howell *et al.*, 2013:76). The real-life experience of chemotherapy-induced nausea will be documented by the patients themselves. This data can be valuable in giving a better insight into the incidence of chemotherapy-induced nausea and if there is an association between patient characteristics and nausea, and/or an association between vomiting and nausea (Grunberg *et al.*, 2013:1).

#### **1.4 Research aims and objectives**

The study's aim and objectives are defined as below.

##### **1.4.1 Research aim**

The aim of this project was to establish the true incidence and patterns of nausea in patients after receiving intravenous chemotherapy in a real-life setting – compared to the ideal of no incidence of chemotherapy-induced nausea.

##### **1.4.2 Specific research objectives**

The above aim was accomplished in two phases:

#### **1.4.2.1 Phase 1: Literature study**

The first phase of this study was a thorough literature study to create an international picture of nausea in patients receiving intravenous chemotherapy with a specific focus on fulfilling the following specific objectives:

- Conceptualised CINV, its incidence, mechanism and prophylaxis from current evidence-based literature
- Reviewed current literature regarding the mechanism of nausea, specifically (related or unrelated to chemotherapy) to understand the incidence and impact thereof, as well as the possible patient characteristics expected with each.

#### **1.4.2.2 Phase 2: Empirical investigation**

During the empirical investigation, the following objectives were pursued:

- Collected data on the incidence and configuration/patterns of CINV during the first three cycles of a patient's chemotherapy; in the acute phase, the delayed phase and the overall phase for each subject; as well as day 7 and day 10 after chemotherapy infusion, including anticipatory nausea before subsequent cycles (data will be collected for cycle 1, 2 and 3 of treatments)
- Measured the time to nausea, the intensity of nausea and the duration of nausea after chemotherapy infusion
- Determined the frequency of use of rescue antiemetics taken on days 1 through 5 (0-120 hours), day 7 and day 10 after chemotherapy infusion
- Investigated the parallel between the incidence of nausea after chemotherapy infusion and anticipatory nausea in subsequent cycles
- Compared the incidence of nausea with the incidence of vomiting for all subjects
- Documented the possible patient-related characteristics placing a patient at a greater risk of chemotherapy-induced nausea for each subject before initiation of treatment.

**Table 1-1: Manuscript results in relation to patient diary with MASCC anti-emesis tool (MAT)**

Objective	Finding	Relevant section of MAT
<p>Collected data on the incidence and configuration/patterns of CINV during the first three cycles of a patient's chemotherapy; in the acute phase, the delayed phase and the overall phase for each subject; as well as day 7 and day 10 after chemotherapy infusion, including anticipatory nausea before subsequent cycles (data will be collected for cycle 1, 2 and 3 of treatments)</p>	<p>The incidence anticipatory nausea</p>	<p>Patient diary: 24 hours before chemotherapy infusion with nausea measured on VAS and vomiting recorded as yes/no question</p>
	<p>The incidence of CINV in acute phase</p>	<p>Patient diary: day 1 (1–24 hours post chemotherapy infusion) with nausea measured on VAS and vomiting recorded as a 'yes/no' question</p>
	<p>The incidence of CINV in delayed phase</p>	<p>Patient diary; day 2, 3, 4 and 5 consecutively (25–120 hours post chemotherapy infusion) with nausea measured on VAS and vomiting recorded as a 'yes/no' question</p>
	<p>Incidence of CINV during day 7 &amp; day 10</p>	<p>Patient diary: day 7 &amp; day 10 with nausea measured on VAS and vomiting recorded as a 'yes/no' question.</p>
<p>Measured the time to nausea, the intensity of nausea and the duration of nausea after chemotherapy infusion</p>	<p>In case of incidence of nausea, the time to nausea, the intensity of nausea and the duration of nausea was measured per patient.</p>	<p>One entry by the patient on the VAS recorded data on intensity (between zero and ten), time to nausea (on 24-hour VAS) and duration of nausea (on 24-hour VAS). Data was entered by patient on day 1, 2, 3, 4, 5, 7 and 10.</p>
<p>Investigated the parallel between the incidence of nausea after chemotherapy infusion and anticipatory nausea in subsequent cycles</p>	<p>Data recorded on the incidence of nausea in the overall phase (day 1–5) was compared to data recorded on the incidence of nausea 24 hour before the next treatment infusion</p>	<p>Patient diary: Day 1, 2, 3, 4, 5, 7 and 10 and one day before next chemotherapy infusion with nausea measured on VAS</p>
<p>Compared the incidence of nausea with the incidence of vomiting for all subjects</p>	<p>Data recorded on the incidence of nausea was compared to the data recorded on the incidence of vomiting during the overall phase</p>	<p>Patient diary: Day 1, 2, 3, 4, 5, 7 and 10 and one day before next chemotherapy infusion with nausea measured on VAS and vomiting recorded as yes/no question</p>
<p>Determined the frequency of use of rescue antiemetics taken on days 1 through 5 (0-120 hours), day 7 and day 10 after chemotherapy infusion</p>	<p>Indicated if rescue medication was taken by individual patients, and what medication was used.</p>	<p>Patient diary: day 1, 2, 3, 4, 5, 7 and 10. "Please record any additional medication taken on day x for nausea/vomiting"</p>

Objective	Finding	Relevant section of MAT
Documented the possible patient-related characteristics placing a patient at a greater risk of chemotherapy-induced nausea for each subject before initiation of treatment.	Recorded gender, age, ethnicity, treatment history, history of morning sickness, history of motion sickness, history of alcohol use and emetogenicity of treatment.	Recorded this information prior to start of treatment on a separate patient information sheet (not part of patient diary).

## 1.5 Research methodology

The research consisted out of two phases: a literature study and an empirical study.

### 1.5.1 Literature review

Topics discussed in the literature review cover the mechanism of CINV (including the receptors and neurological pathways involved), pharmacological management of CINV (with all current and some future available prophylaxis), patient risk-factors influencing CINV, classification of CINV and classification of chemotherapy treatments. Specifically, the mechanism of nausea was studied in evidence-based publications. The study investigated the configuration of nausea in patients receiving intravenous chemotherapy.

A systematic search was conducted using databases such as Medline<sup>®</sup>, Ebscohost<sup>®</sup>, Google Scholar<sup>™</sup> and other available databases. Renowned journals in oncology include: Annals of oncology, Biomed research international, British medical journal, Clinical advances in Haematology & Oncology, European journal of cancer, European journal of pharmacology, Journal of clinical oncology, The New England journal of medicine and Supportive care in cancers among others.

Terms such as ‘emesis’, ‘nausea’, ‘CINV’, ‘quality of life’, ‘chemotherapy’, ‘mechanism of nausea’, ‘mechanism of vomiting’, ‘CINV guidelines’, ‘CINV prophylaxis’, ‘risk factors of nausea and vomiting’ were used to search. Terms were used separately or with Boolean operators, ‘and’ and ‘or’, to use them in combination.

Valuable information was available through reading publications of key opinion leaders in the field, like Dr M Aapro, Dr P Feyer, Dr J Herstedt, Dr P Hesketh, Dr K Jordan, Dr B Rapoport and Dr F Roila to name but a few.

### **1.5.2 Empirical investigation**

This study included all patients receiving intravenous chemotherapy from 8 March 2017 to 15 Sept 2017, at a private oncology clinic in Rosebank. This broad inclusion of patients gave a review of 'real-life' experiences of patients, using a PROM as instrument to collect data. The patients' treatment or surroundings were not influenced by this study, as it was purely observing and collecting of data from patients' self-reported experiences.

The tools used were based on the Multinational Association of Supportive Care in Cancer (MASCC) antiemesis tool (MAT), and were validated and standardised tools that were easy to understand and relatively quick to complete (Roila *et al.*, 2010:232). The MAT is relied upon for its low patient burden and patient-friendly properties, and measures both acute and delayed nausea and vomiting (Molassiotis *et al.*, 2007:148). To make sure patients understood the questions, detailed explanations were provided with an instruction sheet. This study focused on the incidence and configuration of nausea in particular. We wanted to establish whether there was a pattern in the time to nausea, duration of nausea and intensity of nausea. For this reason, the MAT was adapted by the researcher to measure this detail for data collection. The exact same format for MAT was used, but data were collected on a more frequent basis. These tools were integrated into the subject diary (Annexure C).

By collecting the data in this way, it was expected that results seen, be as close to the real-life experience as possible. The project investigated the possibility that there was a difference between the reality of patients experiencing chemotherapy-induced nausea and the perception that chemotherapy-induced nausea is well-managed. The project aimed to establish whether there was any association between patient specific characteristics and/or chemotherapy-induced nausea.

The data on the incidence of nausea regarding intensity and frequency, was evaluated to see if a better perception of nausea can be created and can be used to make recommendations on how (if applicable) to improve the current management in practice.

### **1.6 Study setting**

The study took place in a private oncology centre in Johannesburg, South Africa. The centre has a longstanding and wide referral system from both local and international specialists. The clinic is involved in ongoing research on CINV, including pivotal clinical trials dedicated to registration of products for CINV. The researcher aimed to expand her knowledge in this field in order to make a better contribution to future patients and projects. The population of patients (adults) represented a broad spectrum of cancer diagnoses in patients on medical schemes, as

well as patients paying for their treatment privately. The clinic treats all patients with guidelines from the South African Oncology Consortium (SAOC) which was established to facilitate cost effective oncology treatment to the broader population of South Africa (SAOC, 2001). This wide variety of patients represented a population of 'real-life' patients with standard treatment that could be generalised to other oncology patient populations. Participants for this study were patients diagnosed with cancer who are considered a vulnerable group they were therefore approached and treated with great care. The centre is continuously conducting clinical studies independently or with sponsors and complied with the expected requirements according to the sponsors and the Medicine Control Council (MCC) (now South African Health Products Regulatory Authority [SAHPRA]). All staff members involved with clinical studies in the centre had updated Good Clinical Practice (GCP) training at the time of this study. The clinic and the researcher were covered by professional insurance.

### **1.6.1 Study population**

The clinic served an average of ten new patients diagnosed with cancer per week, including all cancer diagnoses at the time of recruitment for this study. The clinic treats adult patients with cancer to receive hormonal-, chemotherapy-, immunotherapy-, and/or biotherapy treatment. The treatment can be administered orally, intravenously or subcutaneously. This study focused on patients receiving intravenous chemotherapy. Chemo-naïve patients, as well as patients who have received prior chemotherapy, were allowed to take part. Considering the inclusion/exclusion criteria, it was expected that four participants be recruited for the project per week. All patients receiving intravenous chemotherapy could be included in the study, so this formed the study population. The project recruited patients over a seven-month period, from 8 March 2017 to 15 Sept 2017, to reach a minimum of one hundred patients (Cohen *et al.*, 2007:497; Molassiotis *et al.*, 2008:201).

### **1.6.2 Inclusion criteria**

Eligible subjects were recruited using the following criteria:

- All patients diagnosed with cancer, 18 years and older, receiving intravenous chemotherapy (there were no exclusions in disease area, chemotherapy type, number of treatment cycles or lines of cancer treatment previously received).
- Patients must have been able to receive the standard guideline-based antiemetic regimen prior to chemotherapy (no allergies or contra-indications).

- Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, with 0 representing asymptomatic patients, 1 representing symptomatic ambulatory patients and 2 representing symptomatic patients, spending less than 50% of their day in bed (Sorensen, 1993:773).
- Execution of written consent.
- Patient recruitment was active from 08 March 2017 to 15 Sept 2017.

### **1.6.3 Exclusion criteria**

Patients with the following criteria were excluded from the study:

- Patients with a history of moderate or severe nausea or vomiting during prior chemotherapy. If CINV protection is not achieved, the severity thereof can increase nausea and also lead to anticipatory nausea (Rapoport et al., 2016:23).
- Concomitant use of any drug with potential antiemetic efficacy such as this could have masked symptoms of CINV (Chabner et al., 2008:194).
- Vomiting, retching or nausea within 24 hours preceding chemotherapy which could have been an indication of other differential diagnoses (Chabner et al., 2008:190).
- Palliative surgery could lead to multifactorial causes of nausea and vomiting, and patients undergoing palliative surgery within two weeks of study entry (Baines, 1997:1148).
- Depending on the site of irradiation, 50-80% of patients could experience nausea and vomiting, thus patients on concurrent radiation were therefore excluded (Feyer *et al.*, 2015).
- Symptomatic brain metastasis which could also cause nausea and vomiting (Baines, 1997:1148).
- Patients who participated in another study concurrent with this study.

### **1.6.4 Study design**

The study followed a prospective, longitudinal and observational study design. The incidence, duration and severity of nausea experienced by patients receiving intravenous chemotherapy were measured. Nausea is a subjective sensation that cannot easily be measured (Pleuvry, 2015:466). The study used visual analogue scales (VAS) and PROM to get data to resemble

patients' experience as accurately as possible and to ensure data were comparable between patients (Andrews & Sanger, 2014:108; Brink *et al.*, 2012:9).

Each patient's treatment was decided on by the oncologist, according to evidence-based guidelines as per standard practice. The study did not influence the treatment or surroundings of the patient but was purely observational of the patient's experiences. The patients captured their real-life experiences in the diary provided without any influence from the healthcare providers or clinic. Patients were issued with standard antiemetic prophylactic therapy, and rescue medication was issued as per CINV guidelines (Howell *et al.*, 2013:76; Waning & Montague, 2001:45).

The study collected data prospectively. Data collection started after ethical approval of the study.

### **1.6.5 Sampling**

There was no sampling process in this study. During the recruitment period (08 March 2017 to 15 Sept 2017), all patients complying with the inclusion criteria were included in the study. On recommendation of the statistician in Medicine Usage in South Africa (MUSA) at the North-West University (NWU), the study recruited 100 patients over the seven-month period.

## **1.7 Data collection**

The sources and tools used to collect data for this study were patient diaries, patient information sheets and data collection sheets.

### **1.7.1 Data collection tool – patient diaries**

The study used a patient diary based on the MAT tool, developed by members of MASCC. It is a user-friendly and validated tool to collect data universally (MASCC, 2004; Warr *et al.*, 2015:348). The diaries were written in English and were completed by the patients themselves, aided by the definition of nausea as 'the feeling that you might vomit' and vomiting as 'the expulsion of stomach contents'. This was essential to ensure reproducibility of data and to differentiate between other symptoms like dyspepsia, also commonly occurring in chemotherapy patients (Andrew & Sanger, 2014:108).

The patients were trained on how to complete the diaries during the orientation visit and took the diary home after infusion of chemotherapy. Patients documented information in the diaries on the occurrence; duration and severity of nausea during the acute phase (0-24 hours) and the delayed phase (25-120 hours); and day 7 and day 10 after infusion of chemotherapy.

Anticipatory nausea before subsequent cycles was recorded, incidences of vomiting and rescue medication were documented in the diaries as well (Annexure C). Completed diaries for all three cycles optimally contributed to this study, however, patients not feeling up to completing the diary will not be penalised in any way.

The standardised MAT tool measures the incidence of vomiting twice after chemotherapy infusion; once in the acute phase and once in the delayed phase. In addition, it measures the presence or absence of nausea as a 'Yes/No' question on two occasions: in the acute phase and in the delayed phase (MASCC, 2004). The frequency and duration of nausea is not measured with this tool. For the intent of this study, the researcher amended the MAT tool to collect information on a more regular basis. Data on the intensity, frequency and duration of nausea was collected in this way. The format of the tool was not changed. The tool was not pilot tested, as it is a globally validated tool, used for research in CINV. The MAT has been used at this clinic in previous trials.

Anticipatory nausea occurs in certain patients receiving chemotherapy. The factors related to anticipatory nausea are classical conditioning; demographic and treatment-related factors; and anxiety or negative expectancies (Kamen *et al.*, 2014:172). It was therefore possible for participants to experience increased anticipatory nausea by the completion of the diary, and with that the increase of inconvenience. The participants were free to withdraw from this study at any time without consequence. Patients' history of nausea and vomiting were collected at enrolment. The data collected was viewed as 'real-life' experience of the patients and factored in the aspect thereof.

Diary distribution was monitored in conjunction with the clinic diary to follow patient's visit dates. The distribution and collection were tracked on a diary accountability log using subject numbers (Annexure D).

### **1.7.2 Validity and reliability of patient diaries**

The tool used to collect information from the patients was a CINV diary, based on MAT (MASCC, 2004). This was first developed in 2004 by members of MASCC and is a validated, standardised international tool to measure occurrence and intensity of nausea and vomiting, in the acute phase and the delayed phase. The tool is available on the MASCC website under supportive care and is specifically developed to collect uniform data on CINV (MASCC, 2004; Roila *et al.*, 2010:232).

The MAT questions assessed the occurrence and severity of CINV on a categorical scale. The adapted study questions assessed the same questions as the MAT, and in addition, measured

the time to nausea, and the duration and intensity of nausea. The diary was completed by the patients for the acute phase (0-24 hours after initiation of infusion), the delayed phase (25-120 hours after initiation of infusion), on day 7 and day 10 after chemotherapy infusion, as well as anticipatory nausea before subsequent cycles.

Visual analogue scales were used to measure nausea with '0' being no nausea experienced at all, to '10' being nausea at its worst (Annexure C). The adapted MAT diaries used a VAS that represented 24 hours of the day for the seven days investigated. On this scale, the patient marked exactly when nausea was experienced and its intensity (between 0-10). Thus, it provided more detailed information of the variables of intensity and duration of nausea on a daily basis (Molassiotis *et al.*, 2007:148).

The diaries were taken home by the patients to document events as they happened. This contributed to more reliable data as information was not based on memory. The patients had a contact number to the clinic should they have needed any help to complete the diary. The diaries were evaluated by the researcher on return, for missing or unclear data, and clarified with the patient before he left the clinic if necessary.

### **1.7.3 Data collection tool – patient information sheet**

The clinic keeps a file for each patient with updated clinical information on the patient. These files are kept in cabinets in the clinic reception with restricted access. The researcher has access to the patient files. During the orientation visit, the researcher had the relevant patient's file while interviewing the patient for information on medical history and concomitant medication. The patient file was updated with this information.

For this study, the patients' demographic data and clinical information were retrieved from the patient file and recorded on a patient information sheet using the subject number for anonymity (Annexure E). This patient information sheet contained the age, gender, type of cancer, stage of cancer, chemotherapy treatment, prophylactic antiemetic treatment, concomitant medications, co-morbidities and previous chemotherapies received.

### **1.7.4 Validity and reliability of patient information sheet**

The patient information sheet was completed with the researcher during the patient's orientation visit. All information retrieved from the file was verified with the patient, and controlled against source notes from previous reports and results in the file. All new information gained from the patient, regarding concomitant medication and medical history during the interview, were updated in the file.

Data were recorded on the information sheet using a subject number for the purpose of this study. The information sheet was filed with the other relevant documents per subject in a locked cabinet in the researcher's office for the duration of the study.

#### **1.7.5 Data collection tool – data collection sheet**

Data collected from patients during the study was captured on an Excel® spreadsheet. This data was then captured electronically on the Excel® spreadsheet after the orientation visit with each patient. The patients returned their completed diaries on their next visit to the clinic. The information in the completed diaries were captured on the day of return.

The actual diary and patient information sheet were kept in a locked cabinet, while the electronic data were on a password- and virus-protected computer in the researcher's office. This is a computer used by the researcher alone and no other staff members had access to it. Regular backups of data were made on compact disks and stored in a locked cabinet in the researcher's office. Only the researcher had access to the cabinet and computer. The Excel® spreadsheets were used for the statistical analysis.

#### **1.7.6 Validity and reliability of data collection sheet**

Data were captured by the researcher on two separate Excel® spreadsheets. These sheets of data have been compared for erroneous entries. The office used for this purpose had controlled access and could be locked.

### **1.8 Data collection process**

Collecting data for this study did not interfere with the normal flow of the clinic, because the patients and routine visits were used to carry out the study procedures.

#### **1.8.1 Usual routine of the practice**

Patients that are referred to the clinic all follow the same routine as specified in the standard operating procedures of the clinic, this is set out in Table 1-2. This contributes to the management of large numbers of patients by a multidisciplinary team, ensuring optimum clinical and financial outcomes to the patients in a timeous manner. Although all patients are individual cases with individual needs, this management structure contributes to the overall effectiveness of care of all patients. This routine could be adapted at any time should a patient's circumstances call for it.

**Table 1-2: Standard visits followed by new patients at clinic**

<b>Visit in clinic diary</b>	<b>Time line</b>	<b>Description of activities</b>
New patient 1 (NP1) Initial visit	5 working days	Initial visit with oncologist is to determine the appropriate treatment plan. The patient must do diagnostic procedures (blood tests, CT-scans, x-rays, sonars).
New patient 2 (NP2) Second patient visit	3-7 working days	Upon receipt of scan results a treatment plan is submitted to medical scheme (if applicable). Discussion with patient and family (question and answer session).
Treatment Visit	1-3 working days	Patients view orientation video on chemotherapy and start chemotherapy infusion.
Follow-up visit (FU)	5 working days	Follow-up visit with oncologist before commencing with second chemotherapy infusion.

Possible study candidates followed the same timeline as regular new patients (see Table 1-2). This timeline was used to introduce the study to the patients and allowed ample time for consideration, questions and consent as discussed in section 1.8.3.

### **1.8.2 Patient recruitment**

Patients due to receive intravenous chemotherapy at the private oncology clinic in Rosebank, were given the option to participate in this study.

The study recruited patients from 08 March 2017 to 15 Sept 2017. Advertisement brochures, the oncologist and a trial coordinator (registered nurse) at the site were used for the recruitment

of patients. The patients were notified of the availability of the survey at the end of their consultation, if appropriate (NP1, Table 1-2). If a patient showed interest, the option to participate in the study was discussed in the privacy of the trial coordinator's office, where a registered nurse assisted with the independent informed consent process.

The oncologist proceeded with treatment of patients as per formulary and was not involved in the project, other than informing the patients of the availability of the study at the site. Participation was optional, and patients' treatment was not altered in any way due to the nature of the project.

### **1.8.3 Process of obtaining informed consent**

The process of obtaining informed consent was done within the flow of the normal clinic routine for patients with new treatments — as per standard operating procedure of practice (Annexure A). Using the normal management structure of the clinic created a timeline for patients to absorb information and provided the opportunity to communicate with any of the multidisciplinary team regarding any aspect of their disease or treatment. This happened simultaneously with preparation of practical aspects and administration of the treatment plan, without which treatment could not proceed. This management structure served as an organisational tool and patients requiring additional meetings for any reason could have scheduled further appointments at any time.

Patients visiting the clinic had a first consultation with the oncologist (NP1, Table 1-2). During this initial visit, if appropriate, the patient was informed of the project by the oncologist. If the patient showed interest, a further discussion was held in the trial coordinator's office. The intent of the project was described to the patient and the general process discussed. The patient received an informed consent document written in English to take home for perusal and had the opportunity to discuss it with their family or friends (Annexure B). Patients attending the oncology centre are mostly fluent in English. In the event that they did not understand English, a family member or interpreter accompanied the patient.

One week after the initial visit (during the second visit [NP2, Table 1-2]), the patients had the opportunity to indicate whether they were interested in participating in the study. Interested patients had another information meeting with the trial coordinator at this time. The trial-coordinator emphasised that the project was optional, and patients were in no way penalised if they decided not to take part. They were also free to withdraw from the survey at any time. During this discussion, an opportunity was given for further questions. The document was voluntarily signed by the patients once they decided to take part.

The participants were informed of the importance of their compliance and true reflection of their experience when completing the diaries. They were requested to return all diaries timeously after the completion of each cycle. Although patient compliance was important for this study, diary completion and participation were not enforced. The participants did not have any additional expenses for taking part in the study. The researcher committed to protect the identity and privacy of all participants. No patient was penalised in any way if they refused to take part or withdrew from the study for whatever reason. According to the aims and objectives of the study, the patients had to start participation with cycle one of treatment. This gave information on the patterns of nausea in concurrent cycles from initiation of treatment. Patients were however, not expected to complete the study to the end of the treatment if they did not wish to do so.

Signed informed consent forms were kept by the researcher in a locked cupboard at the oncology centre for the duration of the data collection phase. After completion of the data collection phase, the signed informed consent forms are kept at MUSA for seven years. A copy of the signed informed consent form was supplied to the participant.

#### **1.8.4 Orientation of patients on study**

An introduction video regarding the process of receiving chemotherapy is shown to all new patients before commencing treatment (chemo infusion Table 1-1). This is done by oncology nurses as per normal clinic routine. Patients (and their carer/family members, if applicable) who decided to participate in the study, and signed informed consent with the trial coordinator, had a discussion with the researcher to explain the basic principles of CINV and the expectations and rationale of the survey. This discussion took place during their second visit (NP2, Table 1-1) or on their treatment visit before commencement of treatment (Table 1-1). If the patient preferred to discuss the study at any other time, an appointment could be made at both parties' convenience.

Discussions with patients showing interest was arranged so that informed consent was signed before commencement of first treatment infusion and did not delay the initiation of chemotherapy treatment of the patient. The patients were educated in completing the diaries and questionnaires (Annexure C). In the discussion, it was established whether the patient was completely comfortable with the instructions. The patients were issued with the contact details to contact the clinic for issues relating to the study. During this visit, the patient was assigned a subject number for the study. Patient demographics and clinical data were documented (Annexure E).



### **1.8.5 Data management**

The researcher was responsible for the data management described. The diaries and questionnaires were prepared according to patient visits in the appointment diary and issued to patients on the day of their orientation. Subject numbers were used to protect identity of the patients. Patients were educated on how to use the diaries during orientation. They were able to contact the clinic with any uncertainty or questions.

Completed diaries were collected from the patients on their follow-up visit to the clinic one week after chemotherapy, by the researcher. This was done with cycles 1, 2 and 3 for this study, however, the patients were allowed to withdraw at any time if they so choose. Completed diaries were evaluated on return to confirm that information was clear and complete. The information collected from the diaries and questionnaires were extracted for analysis, using a template developed in Microsoft Excel<sup>®</sup> (Annexure F). The computer used was virus- and password protected, and regular back-up of data were made. Hard copies of the diaries were kept in a locked cabinet in the researcher's office for duration of study. A subject diary accountability log was kept regulating the diary distribution and collection (Annexure D).

### **1.9 Statistical analysis**

Statistical analysis was done with the assistance of the statistician at NWU and is summarised in Table 1-3. All statistical analyses were done in Statistical Package for the Social Science (SPSS). All statistical significance was considered with a two-sided probability of  $p < 0.05$ . The practical significance of results was computed when the  $p$ -value is statistically significant ( $p \leq 0.05$ ). Variables were expressed using descriptive statistics such as frequencies (n), percentages (%), means, standard deviations, 95% Confidence interval or medians and interquartile range.

The independent  $t$ -test (Mann-Whitney U-test) was used to compare the difference between the means of two independent groups. The analysis of variance (ANOVA) (Kruskal-Wallis test) was used for more than 2 groups. If a difference was indicated, a Tukey multiple comparison test was performed to determine which groups differ statistically significantly from one another. Cohen's  $d$ -value was used to determine the practical significance of the results (with  $d \geq 0.8$  defined as a large effect with practical significance).

Pearson's Chi-square test was used to determine whether an association existed between proportions of two or more categorical variables. The Cramer's  $V$  statistic was used to test the practical significance of this association (with Cramer's  $V \geq 0.5$  defined as practically significant) (IBM Corp, 2013).

**Table 1-3: Statistical Analysis**

Objective	Independent variable	Dependent variable	Descriptive statistics	Inferential statistics
<b>To measure the incidence of nausea in the acute phase, the delayed phase and the overall phase, day 7 and day 10 after chemotherapy infusion</b>	Phase Acute phase (0-24 hours post-infusion) Delayed phase (25-120 hours post-infusion) Overall phase (0-120 hours post-infusion) Day 7 and day 10 after chemotherapy infusion	Incidence of nausea	Frequencies and percentages	
<b>To measure the time to the first event of nausea after infusion, the intensity of nausea, the duration of nausea.</b>		Time to first event of nausea	Frequencies and percentages	
		Intensity of nausea (Scale of 0-10)	Mean $\pm$ SD	
		Duration of nausea	Median (25 <sup>th</sup> percentile – 75 <sup>th</sup> percentile)	
<b>To establish the incidence of anticipatory nausea in cycle 2 &amp; 3</b>	Nausea after chemotherapy	Anticipatory nausea	Frequencies and percentages Mean and standard deviation or Median and interquartile range	Spearman rank order correlation
<b>To establish whether there is an association between incidence of nausea and incidence of vomiting</b>	Incidence of nausea	Incidence of vomiting	Frequencies and percentages Mean $\pm$ SD Median (25 <sup>th</sup> percentile – 75 <sup>th</sup> percentile)	Spearman rank order correlation

Objective	Independent variable	Dependent variable	Descriptive statistics	Inferential statistics
<b>To establish whether risk factors have an impact on nausea incidence and intensity</b>	Morning sickness during pregnancy (Yes/No) Prone to motion sickness (Yes/No) History of alcohol abuse (Yes/No) Gender (Male/Female) Age	Incidence of nausea Intensity of nausea (scale of 0-10)	Frequencies and percentages Mean $\pm$ SD Median (25 <sup>th</sup> percentile – 75 <sup>th</sup> percentile)	Pearson's Chi-square test  Independent t-test (Mann-Whitney U-test)

## 1.10 Ethical considerations

All study procedures were followed as approved by MUSA.

### 1.10.1 Permission and informed consent

The study was executed with the permission of The Medical Oncology Centre of Rosebank (Annexure G). All subjects signed an informed consent document before commencing with the study (Annexure B).

### 1.10.2 Anonymity

All patients taking part in the study were issued a subject number that was documented on a participant log. This log was kept on the researcher's computer. Only the researcher had access to this computer as it was password protected. All information for the study was collected under the subject number. Only the subject number appeared on the patient information sheets, diaries and data collection sheets. A list of patients and their subject numbers were kept up to date and stored separately. There was no need to protect the identity of the centre, as it is a well-known research site.

### 1.10.3 Confidentiality

The patient site files are kept in cabinets in reception with restricted access for clinic personnel only. The informed consent interview was done by the site trial-coordinator (registered nurse) in the privacy of her office. Participants voluntarily had to sign informed consent to be able to participate in the study. Herewith, they consented to the researcher accessing their clinical files for the research. The orientation discussion was done in the researcher's office for confidentiality. All patients took part anonymously and data records collected for this study were kept in a locked cabinet in the researcher's office, as per practice regulations. No patient was discussed, or information given to other patients or clinic personnel. Computers used to capture

data were password- and virus protected. Using subject numbers for participants contributed to the protection of patients' privacy.

#### **1.10.4 Storing of data**

The storing of data during and after the study is discussed below:

(i) During the study

Hard copies of documents related to the study were kept in an organised manner in a locked cabinet in the researcher's office. The informed consent documents, patient information sheets and completed diaries of patients were filed per patient in the cabinet. This was kept for the duration of the study.

Data collected from the patient information sheets and completed diaries was captured electronically on the researcher's computer, which was password and virus protected. Only the researcher had access to this computer that was in an office with controlled access and could be locked. The subject number allocated to patients during the orientation visit appeared on the electronic records, so patients were not identifiable. Daily back-ups of all electronic data captured were made and stored in the locked cabinet in the researcher's office for the duration of the study.

(ii) After completion of the study

Hard copies of all documents related to the study will be kept secure in locked cabinets at MUSA for a period of seven years. The destruction of the hard copies will take place under the supervision of MUSA's research assistant when this period expires.

Electronic data will be removed from the researcher's computer and stored on a compact disk. This too is kept, together with the hard copies of documents, in locked cabinets at MUSA for a period of seven years, after which it will be destroyed under the supervision of MUSA's research assistant.

#### **1.10.5 Justification of research study**

The study expected to give insight into the incidence of nausea regarding frequency and intensity. The data might establish a possible trend in nausea between different patients. It could give valuable information to indicate the need of larger studies to explore the incidence of nausea, specifically because vomiting is for the most part controlled, due to evidence-based research done on this. Chemotherapy-induced nausea and vomiting is a specific area of interest

to this clinic. Many studies on CINV have been done at this site, contributing to publications and teaching opportunities to improve CINV prophylaxis (Rapoport *et al.*, 2016:23; Weinstein *et al.*, 2016:172).

#### **1.10.6 Respect for research participants**

Participants taking part in the survey were treated with the necessary caution and respect. They were given ample time to ask questions. No information was discussed or divulged other than what was required for the research. Confidentiality was maintained at all times. It was of importance to keep in mind that all participants had a life-threatening disease, and consequently, needed to be considered in every way. Even though it was of importance to collect data as completely and accurately as possible, no participant was pressured for any reason while taking part in the study. Patients could withdraw participation from study at any time. Patient feedback was available to patients on request once the data collection period was complete.

#### **1.10.7 Benefit-risk ratio analysis**

The benefits and risks of the study to the patient were considered during the study design.

##### **1.10.7.1 Anticipated benefits**

- Direct benefits

There were no direct benefits to the patients taking part in this study. The information gained from this study is of considerable value to the better understanding of the incidence of chemotherapy-induced nausea. This could possibly lead to larger investigations aiming to improve this unmet medical need.

- Indirect benefits

The data collected in this study could be valuable to indicate the great unmet medical need of nausea prophylaxis in patients receiving chemotherapy. It could give a better understanding of the incidence of nausea in patients receiving intravenous chemotherapy – as it is currently still unclear. It could serve as an indication for the need of larger studies on nausea, specifically because this is still not clearly understood or managed (Moradian & Howell, 2015:216, Rapoport *et al.*, 2015).

#### **1.10.7.2 Anticipated risks and precautions**

This was a low risk study. Completing the diaries and questionnaires at a time of treatment when patients might not be feeling physically well could have been an inconvenience to the patients. Vomiting and nausea is very distressing and debilitating and could have had an impact on the patient's compliance. However, the tools used to collect data were designed to be user friendly and relatively quick to complete. Other than time and slight inconvenience, there was no risk of harm to the participants. Patients received the clinic's 24-hour emergency telephone number. All issues involving the patient were dealt with priority according to the event.

Risk to the researcher was the added load of co-ordinating and recording all activities of the study in an organised and timeous manner to ensure validity of data. The benefits to the field of study outweighed the risks and/or harm to the subjects and researcher.

#### **1.10.8 Reimbursement to patients**

This was an observational survey. The patients had no additional costs due to participation in this study. The patients experienced the inconvenience of completing the study diary, however, they took part in the study voluntarily and could withdraw at any time. As per routine practice at the site, to avoid undue incentive and influence with treatment, patients were not reimbursed for studies where the patients do not carry additional costs due to participation.

#### **1.10.9 Data management**

The researcher was responsible for the management of the data. To ensure data were accurate, it was compared to source notes in patient clinic files and/or confirmed with patients during the orientation visit. Diaries were evaluated with patients on their return to ensure all entries were clear and complete. Data were captured timeously so possible incorrect or unclear information could be verified immediately. A double entry system was used to ensure accurate capturing of information. Subject logs were kept ensuring diaries handed to patients for completion were collected in an accountable manner in conjunction with the clinic's appointment diary.

#### **1.10.10 Management of the research project**

The project was managed by the researcher (pharmacist) with the assistance of study leaders (Dr JM du Plessis and Ms I Kotze). Planned timelines were followed and tools designed for collecting data were used to ensure validity and reliability of data. Recruitment, keeping of screening lists, subject identification lists, collection of clinical data and variables, collection of hard copies from subjects, evaluation of entered data on diaries, transfer of data from hard

copies to electronic spreadsheets and safekeeping of hard copies and electronic data were done by researcher. Informed consent interviews were conducted by the site trial-coordinator (registered Nurse). After the data collection period, the analysis of data was done with the assistance of the research entity, MUSA, at the NWU with Ms M Cockeran.

#### **1.10.11 Dissemination of research results**

The research results were written as a dissertation for the researcher's Master of Pharmacy degree at the NWU. It was done with the assistance of study leaders, Dr JM Du Plessis and Ms I Kotze. All information gained from this project was made available to subjects who participated if they were interested in an information leaflet. Data from the study were also submitted as an abstract to the South African Society of Medical Oncologists (SASMO) annual convention. It was accepted as an oral presentation at this convention and was presented there in November 2018. The participants' identities were protected, and the analysis was done with the statistical data pool and did not include individual patient information. The results of this dissertation were written in article format. The articles will be available to the clinic where the study was conducted and the researcher intends to publish the articles in peer-reviewed journals. The articles will contribute to the completion of the researcher's degree and can be presented at relevant meetings/congresses.

#### **1.10.12 Role and experience of the members in the research team**

Dr JM Du Plessis was acting as supervisor of this project with Ms I Kotze as co-supervisor. The role of the study leaders was to assist and advise the researcher. Ms M Cockeran, the statistician, further assisted with the statistical data analysis (see attached narrative Curriculum Vitae's regarding qualifications and experience).

Initial informed consent procedures and discussions with patients were done by the site's trial co-ordinator (registered nurse). The researcher (pharmacist) was responsible for all other overall co-ordination of this study. Education on CINV and rescue medication was done by the researcher. The directions on diary completion and data collection were all handled by the researcher. It was the researcher's responsibility to ensure that patients were treated with the necessary respect and that patient identities were protected at all times. The safe-keeping of study material and data were done by the researcher. At the end of the study, the data collection, analysis and writing up of results and dissemination were done by the researcher with the assistance of a statistician, study leaders and other necessary experts. Both the researcher and site trial-coordinator have been working in a clinical trial setting for many years and are familiar with the guidelines and responsibilities.

Dr JM du Plessis, Ms I Kotze, Ms M Cockeran and the researcher have all done their GCP training as well as ethics training. The site trial-coordinator (registered nurse) has updated GCP training.

#### **1.10.13 Conflict of interest**

There could have been possible conflict of interest since the researcher works as a pharmacist at the clinic where the project was implemented. To ensure objectivity, the researcher was not involved in the informed consent process, but for the overall co-ordination of the study.

## CHAPTER 2 LITERATURE REVIEW

### 2.1 Introduction and background to the study

Treating patients with cancer involves much more than eliminating the disease. The quality of life of a patient during and after treatment is as important. The impact on the patient's quality of life – because of the disease and the treatment – needs to be managed during this distressing time (Chu *et al.*, 2014:51; Sommariva *et al.*, 2016:14). Although targeted therapies and immunotherapies are finding increased use in cancer treatment, chemotherapy and radiotherapy remain the standard of treatment for many patients. The effective use of both modalities is limited by a wide range of side effects, of which nausea and vomiting are of the most feared ones (Aapro *et al.*, 2012:233). Chemotherapy-induced nausea and vomiting has been regarded as a single entity for many years, however, current literature shows that control of nausea remains the most important unmet medical need regarding CINV (Gillmore *et al.*, 2014:70). Despite substantial progress in CINV prophylaxis, complete control of CINV, particularly nausea, presenting two to five days after the chemotherapy infusion (the delayed phase [see section 2.4.1]) has proven difficult (Chasen *et al.*, 2017:86).

Since nausea is a perception, it complicates the defining of nausea as different feedback could be received from different subjects (Howell *et al.*, 2013:85). The perception of nausea can be misinterpreted between patient and healthcare provider, and gaps exist between the patient's symptom experience and the clinicians' symptom awareness (Andrews & Sanger, 2014:4). Nausea is often perceived as being of secondary importance by investigators (Rha *et al.*, 2016: 4559).

Appropriately designed tools that can measure the incidence, intensity and the duration of nausea need to be created. A literature search shows more than 20 instruments exist to measure CINV, but only one measured nausea in particular (Wood *et al.*, 2011). To avoid misinterpretation, the tools should be self-reported instruments completed by the patients. However, the design must be able to analyse data between patients to offer a valid and reliable clinical assessment (Lindley *et al.*, 1992:338; Molassiotis *et al.*, 2007:148).

The research done on nausea has been hampered by the lack of suitable animal models that replicate human behaviour accurately (Babic & Browning, 2014:39). The investigation of pathways of nausea and their pharmacology relies largely, upon the use of appropriate animal models. However, it is questionable whether these models are suitable (Andrews & Horn, 2006:110). Limitations that exist with animal models are the absence of a vomiting reflex in some species, the inability of animal models to identify nausea, as well as potential welfare

issues (Ng *et al.*, 2011:162). Nausea produced through visual stimulation, brain processing patterns of nausea, potential biomarkers of nausea and other methods used to imitate nausea are used, but no widely accepted model for preclinical testing exists (Horn *et al.*, 2014:4; Sanger & Andrews, 2006:13).

Many confounding factors can lead to nausea and it is difficult to distinguish the origin of the symptom. The aetiology of nausea is not only physical (the administration of toxins, exposure to radiation, gastrointestinal disease, pregnancy and motion sickness), but also psychological (stimuli such as stress, extreme emotional reactions and conditioned smell and taste aversions (Balaban *et al.*, 2017:6; Smith *et al.*, 2012:87). More understanding of the complex multifactorial process of nausea is still needed (Jordan *et al.*, 2015:1081).

Clarification on the subject nausea has been pursued from the earliest times (Andrews & Sanger, 2015:2). Without intending to, much progress has been made in the understanding and control of vomiting, with still very little understood about nausea (Sommariva *et al.*, 2016:13). It is only of late that nausea has been separated as a different entity and it is now suspected nausea must be approached differently than that of vomiting (Pirri *et al.*, 2013:736). This study focuses on nausea in particular, in a quest to better understand the prevalence and configuration of nausea in patients receiving intravenous chemotherapy.

## **2.2 The history of nausea**

*“T’is profitable for man that his stomach should nauseate or reject things that have a loathsome state of smell.”*

*~ Robert Boyle 1627-1691 ~*

Nausea has been described in Greek and Egyptian medical texts since the earliest times. Works of Egyptian medical knowledge dating from 1500 before Christ (BC) can be found in the university library of Leipzig. The work consists of collections of diagnosis and remedies, some of which are probably as much as 2000 years old, according to the *Ancient Egyptian medicine: The Papyrus Ebers* (Stern *et al.*, 2011:4).

The understanding and description of nausea has changed over several millennia, making the defining of nausea difficult as it has many triggers and can build up slowly or rapidly and the prodromal signs and symptoms can vary (Balaban & Yates, 2017:6).

In Greek, *asao* means disgust. As primary mode of travel was by ship, it is here that nausea was commonly experienced, hence the Greek word *naus*, meaning ship (Andrews & Sanger, 2014:108). The diverse collection of definitions over time includes words like disgust, loathing, uneasiness, sick, unpleasant, pain and stress. Today the standardised definition for nausea, according to MASCC, is 'the feeling that you might vomit' (MASCC, 2004).

Nausea is a subjective sensation of humans that is present in a diverse range of diseases and occurs more commonly than vomiting or retching (Andrews & Horn, 2006:101; Feldman *et al.*, 1988:721). Food poisoning, gastrointestinal obstruction, motion sickness, inflammatory bowel diseases, peptic ulcers, hepatitis and adverse events of some medications are a few of numerous causes of nausea. Symptoms of nausea dramatically affect patients' quality of life, employment-productivity and economic burden (Bashashati & McCallum, 2014:80).

It has been accepted for over a century, regardless of the difficulties in clarifying the precise neurocircuitry involved in nausea (and vomiting), that the precise location of these neurocircuits involves several structures within the hindbrain, including the area postrema, the nucleus tractus solitarius (NTS), the dorsal motor nucleus of the vagus, the reticular formation and the ventrolateral medulla (see section 2.3) (Babic & Browning, 2014:39). Despite this knowledge, the literature devoted to describing the areas involved in the genesis, maintenance and resolution of nausea is scarce and insufficient (Farmer *et al.*, 2015:1184). Much of the older key information is in books that are hard to locate and the current medical challenge we face today is nausea not being recognised as a separate entity and most research being devoted to vomiting (Aapro *et al.*, 2012:1990; Andrews & Sanger, 2014:4).

Until the early 1970s, the sensation of nausea was frequently dismissed as merely a passing phenomenon (Slomski, 2013). Substantial progress has been made over the past two decades in the pharmacologic prophylaxis and treatment of nausea and vomiting induced by chemotherapy. International clinical guidelines for preventing CINV are frequently updated and reflect the advances in antiemetic therapy (Burke *et al.*, 2011:132; Chasen *et al.*, 2017:86). Despite the introduction of more effective antiemetics (high dose metoclopramide) in the 1980s, followed by the first-generation serotonin antagonists in the 1990s and the NK-1 receptor antagonist in 2003 (see section 2.6), CINV – and nausea in particular – continues to exact a toll on patients with cancer and their families (Bloechl-Daum *et al.*, 2006:4472, Hawkins & Grunberg, 2009:54, Navari & Aapro, 2016:1359).

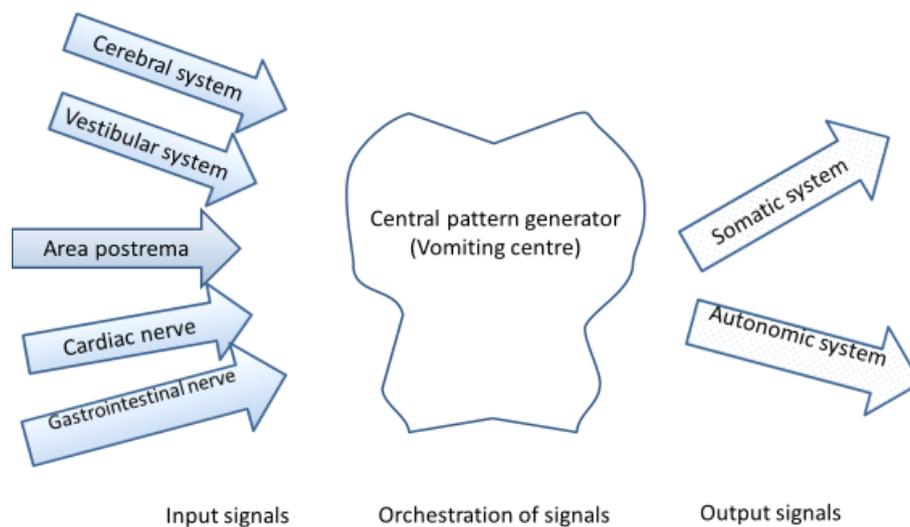
## 2.3 Pathophysiology of nausea

Different systems are involved in the creation of nausea: the central nervous system (CNS), the autonomic nervous system, the endocrine system and the gastrointestinal system (Andrews & Sanger, 2014:112).

The complex event of nausea can be simplified into a three-step process:

- Input signals from a variety of emetic stimuli are sent from different parts of the body to the brain.
- The central pattern generator or vomiting centre receives and processes all these signals.
- Output signals are returned from the central pattern generator to different parts of the body.

This process is illustrated and will be discussed in more detail in sections 2.3.1 and 2.3.2 (Andrews and Horn, 2006:108).

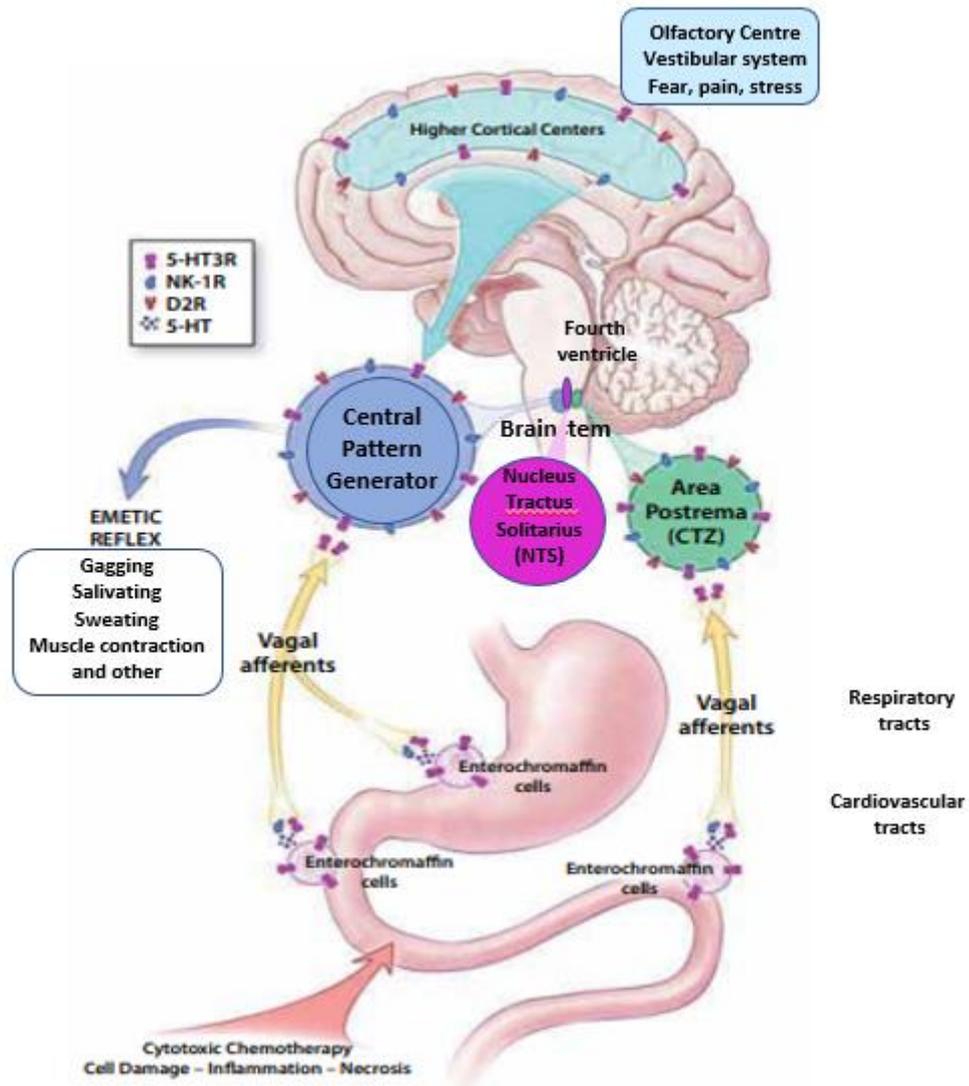


**Figure 2-1:** A simplified layout of the complex event of nausea and vomiting in the body

The sensory experience of nausea and the associated physiological changes involve bi-directional interactions between the CNS, the autonomic nervous system and the endocrine system (Andrews & Sanger, 2014:3; Farmer *et al.*, 2014:1184). The human body has an interoceptive system whereby the cells in the body can send signals and perceive information, communicating the condition of the tissue in the body, via the parasympathetic nerves (vagal afferents) to the NTS (Craig, 2003:500).

### **2.3.1 Central nervous system and the nucleus tractus solitarius**

The central nervous system plays a critical role in the pathophysiology of CINV, receiving and processing multiple signals received from different parts of the body as demonstrated in Figure 2-2. (Grunberg *et al.*, 2013). The areas involved in the receiving and generation of nausea and vomiting stimuli are the chemo trigger zone in the area postrema, the NTS and the vomiting centre in the reticular formation (Babic and Browning, 2014:39; Chin *et al.*, 2006:1153). These areas are all located in the medulla oblongata in the brainstem (Smith *et al.*, 2012:87).



**Figure 2-2: Activation of the emetic response from different input signals**

The blood-brain barrier protects the brain by regulating compounds' movement across the barrier from the peripheral circulation (Tran, 2011). In the brainstem, at the bottom of the fourth ventricle of the brain, is the area postrema (Yates & Miller, 1998:398). The area postrema is a circumventricular organ that lacks a blood-brain barrier and is consequently not isolated from the peripheral circulation (Babic *et al.*, 2014:42). This area in the area postrema is therefore capable of detecting emetic agents in both the blood and the cerebrospinal fluid and is called the chemo trigger zone (Chu *et al.*, 2014:49; Shinpo *et al.*, 2012:98). Activation of the area postrema probably leads to nausea and vomiting through its projection to the neighbouring NTS (Miller & Leslie, 1994:301).

The NTS plays a leading role in creating, perceiving and reacting to the feeling of nausea (Hesketh, 2008:2484). It is located inside the brainstem and contains over a million synapses (the point at which impulses pass from one nerve to another [Vaugh & Grant, 2014:144]). These bundles of synapses act as a gateway to the brain for visceral stimuli from the cardiovascular, respiratory and intestinal tracts (Andresen & Kunze, 1994:93; Zafra, 2017:90). The vagus nerve (cranial nerve number ten) is the rapid information transmission pathway through which visceral stimuli reach the NTS (Traub *et al.*, 1996:874). The NTS is neurochemically diverse and contains more than 40 neuroactive substances and receptors, influencing all major regions of the brain (Miller & Leslie, 1994:301). Signals are sent from the body with encoded information to the NTS. Once received, the NTS processes this information, conserves the information and redirects the information to create the corrective motor- or sensory response in the body (Lang & Marvig, 1989:92). Very little is known about the processing of information in the NTS. However, it is clear that the responses to impulses are rapid. The synapses inside the NTS shows plasticity, indicating that the processing is not a fixed mechanism, but modulatory impulses can influence the outputs from the NTS (Chen & Bonham, 2005:535).

According to Babic and Browning (2014:39), the possible existence of a vomiting centre located in the brainstem has been published as early as 1891 by Thumas. The vomiting centre is the focal point from where the elaborate series of events experienced during nausea is orchestrated (Hesketh, 2008:2483; Navari, 2013:251). The terminology 'vomiting centre' has been replaced by the term 'central pattern generator', as there is no well-defined discrete vomiting centre (Pleuvry, 2014:462; Smith *et al.*, 2012:88). The central pattern generator is a diverse population of loosely organised neuronal areas within the medulla, activated by input stimuli received from all regions of the body, subsequently sending output signals to many parts of the body, creating the symptoms associated with nausea (symptoms of nausea are discussed in section 2.3.2 and section 2.4.3) (Hawkins & Grunberg, 2009:56; Hornby 2001:106). The central pattern generator is located in the reticular formation in the medulla (Navari, 2013:251).

The reticular formation is interconnected nuclei in the medulla, forming ascending and descending pathways between the brain and the spinal cord, to the rest of the body (Yates *et al.*, 1994:197). Neurons that coordinate vomiting are distributed through the reticular formation from the NTS to the medulla (Yates *et al.*, 1998:398).

Input signals are not only received from the autonomic nervous system and the gastrointestinal system, but also from the cerebral cortex in the central nervous system (Andrews *et al.*, 2014:7). The central pathways for nausea are impulses sent via the NTS to the 'higher' regions of the brain and involve the hypothalamus, conditioned taste aversions and higher projections of

information received from organs, olfactory- and vestibular pathways (Horn *et al.*, 2014:4; Stern *et al.*, 2011:17). According to Farmer (2015:1183), the gaps in knowledge of the CNS involvement in nausea is probably due to significant methodological challenges in studying nausea in the confines of the brain imaging environment.

The central pathways involved with nausea involve the following systems:

- (i) The hypothalamus is a small area in the frontal brain and is important in the regulation of behaviour and responses to stress (Bashashati *et al.*, 2014:85; Bergstrom *et al.*, 2004:1007). Physical changes such as inflammation, infection, pain or psychological changes such as emotional stress, activates the hypothalamus (Chu *et al.*, 2014:49). During the sensation of nausea, the hypothalamus regulates key physiological changes in the body namely: anorectic effects, the increase in vasopressin in the plasma and the modulation of autonomic outflow to the sympathetic system. These changes are responsible for the symptoms experienced that accompany nausea (Andrews *et al.*, 2006:109).
- (ii) Conditioned taste aversions are a learned avoidance (response) of specific food related to specific taste or illness (stimulus). Many species, including humans, show conditioned taste aversions to foods or flavours associated with toxicosis (Andrews *et al.*, 2006:103; Balaban *et al.*, 2017:10). Most research related to nausea that has been performed on animals, make use of conditioned taste aversions because it is uncertain whether animals experience nausea. Conditioned taste aversions after a noxious stimulus is used as an indirect index that nausea was produced by that stimulus (Feldman *et al.*, 1988:722).
- (iii) Nausea is a subjective sensation that is associated with objective physiological changes as well as neuronal activity in the brain with region-specific increases and decreases in activity. In the particular brain regions, this combination leads to sensory discrimination (awareness) of nausea, cognitive evaluation (thinking about nausea) and affective, motivational behaviour (anorexia or avoidance of the substances causing the change) (Farmer *et al.*, 2015:1184). Higher projections involve a person's internal sense of wellbeing and alertness to change in your body, usually involving an attempt to return the body to the normal state (Craig, 2003:500). A stimulus within the 'higher regions' of the brain (fear, anticipation, brain trauma, sudden raised intra-cranial pressure), can evoke the emetic reflex. The mechanisms involved are poorly understood. Such stimuli often evoke vomiting with little or no prior retching or nausea (Sanger & Andrews, 2006).

- (iv) Olfactory pathways lead to conscious perception of odours or smell and are (along with taste and sight) the first line of defence aimed at preventing the ingestion of toxins (Pleuvry, 2015:462; Smith *et al.*, 2012:89).
- (v) The vestibular system, which is located within the inner ear, is involved in providing a sense of balance. The apparatus of the middle ear reacts to position change and can trigger nausea and vomiting (Garrett *et al.*, 2003:32; Hamling, 2011:322). While the vestibular system might not be a primary pathway in the development of CINV, vestibular disturbances are implicated in the exacerbation of CINV (Marx *et al.*, 2017:143).

Every person may require a different degree of stimulation to the emetic centre (by the central pattern generator) to reach the threshold of nausea and vomiting, thereby resulting in differing individual responses to the same stimuli (Janelsins *et al.*, 2013:759).

### **2.3.2 Autonomic nervous system and gastric dysrhythmias**

The peripheral nervous system is made up of the somatic nervous system (the voluntary skeletal muscle) and the autonomic nervous system (the involuntary smooth muscles). The autonomic nervous system unconsciously aims to maintain a state of physiological balance or homeostasis in the body (Cardinali, 2018). It regulates bodily functions such as the heart rate, digestion, respiratory rate, pupillary response, urination and reflex actions such as vomiting (De Zambotti *et al.*, 2018:85). Autonomic reflexes respond to physiological and environmental changes such as heat, cold, exercise, eating a meal or standing up (Waterhouse & Campbell, 2017:273).

For the awareness of nausea and vomiting to occur, the physiological responses and changes during the event are communicated from the body to the central nervous system via autonomic nerves (Balaban & Yates, 2017:6). Autonomic efferent nerves send signals from the brain to the body and autonomic afferent nerves carry information from the body to the brain (Howland, 2006:11).

Autonomic afferent nerves play a key role in induction of nausea and vomiting and are a target for antiemetic drugs, while the autonomic efferent nerves are responsible for many of the visible and visceral motor phenomena that accompany nausea and vomiting (looking pale, cold sweating, increased heart rate, respiratory arrhythmia and salivation) (Stern *et al.*, 2011:77).

The autonomic nerves of primary interest in nausea and vomiting are the abdominal vagus nerve, evoking a gag reflex, retching and coughing; and the greater splanchnic nerve evoking

abdominal muscle contraction and a creation of 'gut' pain (Grabouskas & Owyang, 2017:74; Grundy, 2002:2; Stern *et al.*, 2011:107).

Nausea is often a prodromal symptom of vomiting although they are separate physiological processes and both engage complex CNS and autonomic nervous system neurocircuitry that is still not yet clearly understood (Babic & Browning, 2014:39).

### **2.3.3 Endocrine system**

The endocrine system is a control system of ductless glands that release their secretion directly into the intercellular fluid or into the blood (Johnstone *et al.*, 2014:42). These secretions (hormones) act as messengers and are carried by the bloodstream to different cells in the body, which interpret these messages and act on them. The autonomic nervous system (section 2.3.2) acts together with the endocrine system to maintain an internal balance (homeostasis) in the body (Craig, 2003:500; Waugh & Grant, 2014:214). The hypothalamus is the main governing centre for homeostatic functions, managing and co-ordinating the glands and organs to keep an internal balance in the body (Cardinali, 2017).

In situations that are stressful to the body, various hormones are released from an endocrine gland in the brain, called the pituitary (Bashashati & McCallum, 2014:81; Otto *et al.*, 2006:17). Different stress hormones are associated with the sensation of nausea; adrenocorticotrophic hormone (ACTH), cortisol and vasopressin (ADH), and gastro-enteropancreatic peptides (vasoactive intestinal polypeptide, pancreatic polypeptide, gastrin, and secretin) (Balaban & Yates, 2015:12; Farmer *et al.*, 2015:1185; Otto *et al.*, 2006:19).

It has been established that there exists a correlation between the plasma levels of some stress hormones and the intensity of nausea. However, it is not clear whether the stress hormones are responsible for the sensation of nausea, or if they are indicators of the stressful nature because of the nausea (Andrews & Horn, 2006:107; Andrews & Sanger, 2014:12).

The possibility to use certain stress hormones as biomarkers for nausea (due to motion) has been suggested decades ago (Drummer *et al.*, 1990:821; Kohl, 1985:1158). The ideal biomarker for nausea would have to be released in proportion to the severity of the nausea, and it would have to be easily measured, without bias (Kenward *et al.*, 2015:38). However, plasma endocrine monitoring needs carefully controlled conditions to be able to identify consistent changes associated with nausea, which is unlikely in patients due to variable baseline levels of hormones between individuals and different physiological states (Andrews & Horn, 2006:197; Balaban *et al.*, 2017:12).

Biomarkers for nausea could potentially be used to refine animal models used in studies of antiemetic agents, as well as increase the validity and translation to findings in humans (Farmer *et al.*, 2015:1185). The identification of biomarkers for nausea could assist in understanding why nausea is such a common dose-limiting toxicity (Andrews & Sanger, 2013:2).

## **2.4 The treatment of cancer and chemotherapy-induced nausea**

Chemotherapy describes the use of synthetic chemicals to destroy cancerous cells in the body (Cassidy *et al.*, 2010:90). The body perceives these chemicals as toxic and uses the age-old self-protection mechanism of nausea to protest (Bashashati & McCallum, 2014:80). This section describes the treatment of cancer with chemotherapy and consequent chemotherapy-induced nausea.

### **2.4.1 The mechanism and cycles of chemotherapy**

Treatment plans are based on years of research. Oncologists use the best combination of drugs, for a specific kind of cancer, based on the results of these trials. A course of chemotherapy treatment is divided into four to eight cycles. A cycle is the time between one round of treatment until the start of the next. Each cycle is given every two to three weeks – with rest periods in between to allow the patient's body to recuperate from toxic effects of the treatment (Cancer Research UK, 2018; Cancer; Cencer.Net, 2018).

### **2.4.2 Measurement of nausea**

Patient-reported outcome measure is a tool used to report a symptom experienced by a patient, with the reporting coming directly from the patient (Moradian & Howell, 2015:234).

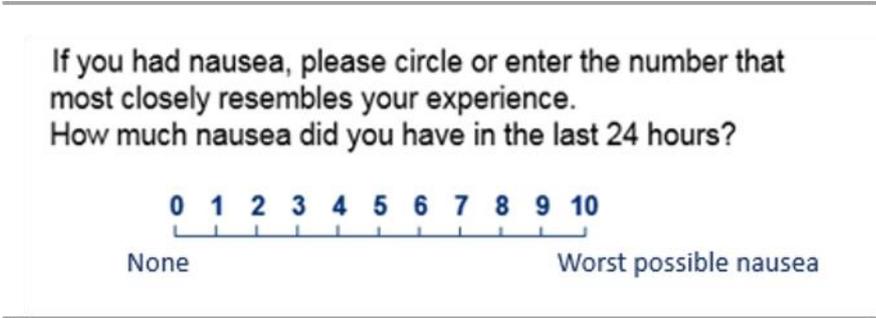
Nausea is a multidimensional experience including physical-, emotional- and psychological components (Howell *et al.*, 2013:77). Furthermore, nausea is a subjective sensation and assessments are entirely based on the healthcare providers' opinion – which can lack objectivity and precision (Sommariva *et al.*, 2016:14). A wide gap exists between clinician and patient perceptions of nausea, particularly with delayed nausea (Rha *et al.*, 2016:4559; Vidall *et al.*, 2015:3304).

A PROM is more precise for individual tracking of nausea and improved quality of clinical care through early identification of nausea (Basch, 2010:865; Howell *et al.*, 2013:85).

Tools have been available for many years to assist in monitoring the frequency, duration and severity of CINV, unfortunately, none of these tools include nausea as a separate entity, reported in the acute and delayed phase, respectively (Wood *et al.*, 2011).

The VAS is a self-reporting scale designed for use in measuring subjective experiences such as pain and nausea, and is illustrated in Figure 2-3 (MASCC, 2004). The VAS is a 100-millimetre line on which zero millimetre represents 'no nausea' and 100-millimetres 'worst possible nausea' (Kenward *et al.*, 2015:38). The Multinational Association of Supportive Care in cancer has developed MAT, incorporating the VAS (Molassiotis *et al.*, 2007:150; Warr *et al.*, 2015:349).

With the experience of delayed nausea, patients are typically not seen in the clinic during this time period, leading to difficulties in assessing the severity and impact of nausea in a patient's daily life (Rapoport, 2017). The MASCC antiemetic tool defines nausea and vomiting as separate entities and distinguishes between acute and delayed phases (Warr *et al.*, 2015:349).



**Figure 2-3: Visual analogue scale as used in MAT**

Delayed phase CINV has been found to have a greater impact on quality of life than CINV experienced in the acute phase, highlighting the importance of being able to measure impact of nausea in the different phases (Chasen *et al.*, 2017:86). Figure 2-4 shows an extract of the Functional Living Index – Emesis (FLIE) that is a validated PROM assessing the impact of CINV on the quality of a patient's daily living. Responses are marked by the patient on a seven-point, one-hundred-millimetre VAS, with anchors of 'a great deal' and 'not at all'. Higher scores correspond to less effect on daily activities. The FLIE questionnaire is completed twice; on day two, reflecting the acute impact of CINV on daily life activities during the first twenty-four hours after chemotherapy infusion and again on day five, reflecting the delayed impact (days 2 – 4 after chemotherapy infusion) of CINV on daily life activities (Chasen *et al.*, 2017: 86; Martin *et al.*, 2003:1396).

It is important to use a standardised definition of nausea in PROM to achieve reproducibility of data and to differentiate between related symptoms such as dyspepsia, bloating or visceral pain (Andrews & Sanger, 2014:4). The patient diaries in this study used 'the feeling that you might vomit' (see section 1.7.1).



dropped to around 50% of patients receiving intravenous chemotherapy. He also reported rates of breakthrough nausea in the delayed phase range from 26-30% when patients use current GCCP.

The experience of nausea in a previous cycle can contribute to the nausea intensity in the subsequent cycle, with nausea usually peaking on the third day after chemotherapy infusion (Rha *et al.*, 2016:3379). Anticipatory nausea occurs in 5-8% before subsequent cycles of chemotherapy (Chan *et al.*, 2015:283). In a study reporting on the incidence of CINV in women with breast cancer, 77.3% of patients reported feeling nausea at least once during their treatment (de Oliveira *et al.*, 2015:119).

Despite the availability of antiemetic treatment options, a review done by Sommariva *et al.* (2016:20) showed that CINV continues to have a negative impact on the health-related quality of life (HRQoL) of patients, with nausea not only having a greater impact on quality of life than vomiting, but more patients experienced an impact on daily life from nausea than from vomiting (Bloechl-Daum *et al.*, 2006:4479, Decker *et al.*, 2006:35). Patients frequently cite nausea and vomiting as among the most unpleasant and distressing side effects of chemotherapy (Cohen *et al.*, 2007:498). The side effect of nausea was ranked worse than fatigue, depression or the impact of chemotherapy on their family or partner and may be present for up to seven days after chemotherapy dosing (Chasen *et al.*, 2017:85; Martin *et al.*, 2003:522).

Nausea is, however, difficult to describe as it is a subjective symptom and not quantifiable like vomiting. Vomiting subsides once the patient has been sick, but little can be done to ease nausea, with triggers for nausea – like food and aromas – difficult to avoid (Vidall *et al.*, 2015:3302). A survey done by Lindley *et al.* (1992:337) showed patients' quality of life can be reduced by as much as twenty percent in patients who experienced CINV compared to symptom free patients. Additionally, symptoms of CINV impact the patients' ability to maintain normal function and creates, in their perspective, hardships on both themselves and their families (Hassan & Yussoff, 2010:1523).

Patients with severe nausea reported negative effects on their activities of daily living, social life and quality of life (i.e. not going out with friends, feeling irritable and not wanting to be bothered). Concurrent symptoms occurring with nausea included sleep disturbance, fatigue, bloating, sweating, weakness, dizziness, headache and flu-like symptoms. Feeling hot and cold, burping, a 'feeling to swallow', regurgitation, intolerance of smell, taste disturbance, loss of appetite and decreased physical activity added to the debilitating effect on patients' daily life (Abe *et al.*, 2015; Ballatori & Roila, 2003; Burke *et al.*, 2011:132; Molassiotis *et al.*, 2008:449).

Nausea and vomiting that is not adequately controlled may lead to malnutrition, dehydration and hydro-electrolytic imbalance which is a major cause of morbidity and mortality in patients diagnosed with cancer (de Oliviera, 2015:118; Farrell *et al.*, 2013:). In addition to lowering the patients' quality of life, it burdens the healthcare facilities with increased costs of lengthened therapies, longer hospital stays and increased consultation times (Davidson *et al.*, 2012). Patients who experience CINV may be discouraged from completing their chemotherapy regimen (Aapro *et al.*, 2012:1987). Nausea can cause patients to experience increased anxiety and dissatisfaction with the clinic experience (Garrett *et al.*, 2003:31). Nausea and vomiting have also been associated with shortened survival (Glare *et al.*, 2008:2576). Furthermore, once CINV is experienced, anticipatory CINV may ensue during subsequent cycles of chemotherapy (Boccia *et al.*, 2016).

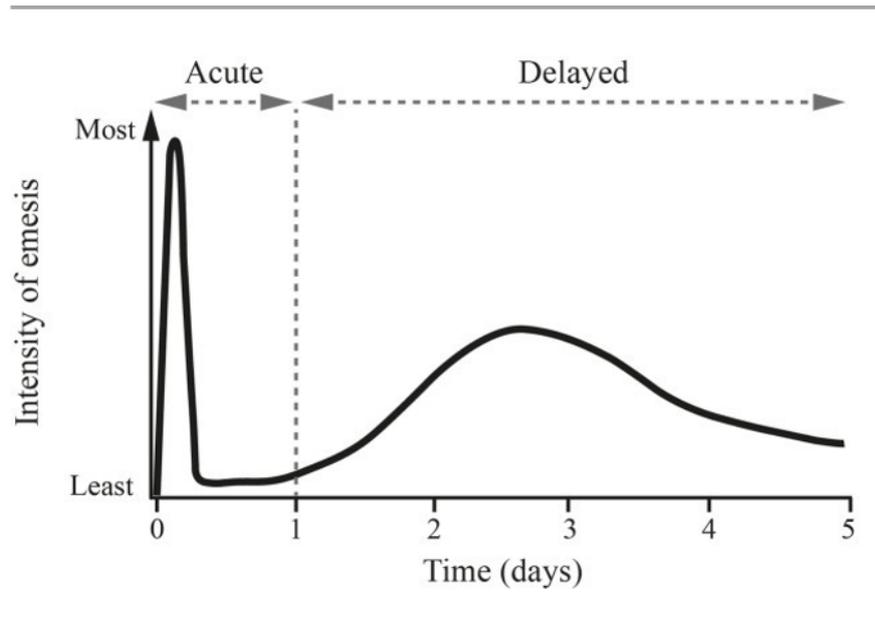
Although newer drugs like NK-1 receptor antagonists have shown to improve the negative impact of CINV in patients' daily lives, nausea remains a key quality of life problem for patients and needs to be assessed and treated on its own rather than in combination with vomiting (Chasen *et al.*, 2017:89; Farrell *et al.*, 2013:65).

#### **2.4.4 Chemotherapy-induced nausea versus CINV**

The first part of Chapter 2 described the history, pathophysiology and impact of nausea (see section 2.1 to section 2.4.3) and was done by using literature written on nausea specifically. As discussed in section 2.2, most published literature on chemotherapy-induced nausea, regards CINV as one entity. For this reason, the second half of Chapter 2 will elaborate on attributes of CINV due to the absence of information in the literature on chemotherapy-induced nausea only.

#### **2.5 Phases of CINV**

Chemotherapy-induced nausea and vomiting typically presents in two phases over a five-day period, namely: the acute phase and the delayed phase. An adapted version of the description by Travorath & Hesketh (1996:640) of the pattern of emesis (with both an early and delayed period) is illustrated in Figure 2-5. This illustrates the biphasic pattern of emesis after the administration of high-dose cisplatin (a high emetogenic chemotherapy [HEC]) with the maximum intensity seen within the initial 24 hours followed by a second peak of less intense CINV on days two and three (Rapoport, 2017).



**Figure 2-5: The bi-phasic pattern of cisplatin-induced emesis**

Acute CINV occurs within one to two hours of chemotherapy administration and can last for up to 24 hours while delayed CINV presents more than 24 hours after chemotherapy administration (Chiu *et al.*, 2016:2382; Rapoport, 2017). Delayed CINV can appear even in the absence of acute CINV and remains to be an unanswered medical need for patients diagnosed with cancer (Grunberg *et al.*, 2004:2261). The acute phase appears to be mediated primarily by serotonin pathways, whereas delayed CINV is mediated by substance-P (see section 2.6) (Hawkins & Grunberg, 2009:56).

Several antiemetic guidelines are available for the prevention of CINV in both the acute- and delayed phase (Boccia *et al.*, 2016). Good control of CINV during the acute phase has been shown to decrease the risk of delayed emesis. Conversely, failure of prophylaxis during the first 24 hours after chemotherapy is high predictive for delayed emesis during the same cycle (Aapro *et al.*, 2012:233).

Chemotherapy-induced nausea and vomiting can also be classified as anticipatory CINV, breakthrough CINV or refractory CINV (Navari, 2013:252). Anticipatory CINV (experienced by up to 40% of patients) is a conditioned response occurring because of prior poor control of CINV in previous chemotherapy treatments (Moradian & Howell, 2015:218). Potential conditioned stimuli for anticipatory nausea can include the sight and smells of the clinic, the nurses and the treatment room (Kamen *et al.*, 2014:173). Inadequate emesis control may lead

to anticipatory CINV, which is a challenging condition to treat and potentially refractory to standard medication (dos Santos *et al.*, 2012:1280).

The failure to control CINV effectively with prophylactic antiemetics is defined as breakthrough CINV (Chiu *et al.*, 2016:2381; Feyer & Jordan, 2011:33). Refractory CINV recurs in subsequent cycles of therapy when all previous preventative and rescue treatments failed (Jordan *et al.*, 2014:200).

Prevention of CINV on the first cycle of chemotherapy remains an important goal of antiemesis therapy because it may help to minimise CINV during subsequent cycles and decrease the incidence of delayed CINV (Burke *et al.*, 2011:132). Despite the availability of multiple antiemetic agents and treatment guidelines, there is still an unmet need for adequate prevention of delayed CINV in patients receiving moderately emetogenic chemotherapy (MEC) and HEC (Boccia *et al.*, 2016).

## **2.6 Pharmacology – receptors and neurological pathways involved with CINV**

The pathophysiology of CINV is known to be a complex multifactorial process involving numerous neurotransmitters and receptors (see section 2.3 ) (Hesketh *et al.*, 2015). An understanding of the main neurotransmitters involved is helpful in assessing and treating patients with nausea and vomiting because antiemetics are predominantly neurotransmitter blocking agents. They are effective at different receptor sites, and therefore treat different causes of nausea and vomiting (Baines, 1997:1148).

The main approach to control emesis is to identify the active neurotransmitters (serotonin and substance-P) and their receptors 5-HT<sub>3</sub> and NK-1 (dos Santos *et al.*, 2012:1281). Efforts to prevent and treat CINV have been directed at blocking these neurotransmitter receptors.

Substantial progress in our understanding of the neural mechanisms underlying CINV has led to the development of high effective therapeutic approaches (Chasen *et al.*, 2017:86).

### **2.6.1 First generation serotonin receptor antagonists (5-hydroxytryptamine-3 [5-HT<sub>3</sub>])**

Serotonin receptors are important neurotransmitters involved in CINV and were added to the antiemetic arsenal in the early 1990s (Burke *et al.*, 2011:131). The highest levels of 5-HT<sub>3</sub> receptor binding sites in the human body are within the dorsal vagal complex within the brainstem (Barnes *et al.*, 2009:279). This region comprises of the NTS, AP and the dorsal motor nucleus of the vagus nerve, which are key to the coordination of the vomiting reflex (see section 2.3). Antagonism of these 5-HT<sub>3</sub> receptors, therefore, contributes to the antiemetic action of 5-HT<sub>3</sub> receptor antagonists.



Among the various types of antiemetic agents, 5-HT<sub>3</sub> receptor antagonists have become established as the cornerstone of therapy for CINV prophylaxis due to their efficacy and low incidence of side effects compared with alternatives (Aapro *et al.*, 2006:1442). By 2003, 5-HT<sub>3</sub> RAs used either alone or in combination with a corticosteroid, have almost completely replaced all other antiemetic regimens (Geling & Eichler, 2005:1290). Salvo *et al.* (2012:408) showed in a meta-analysis the superiority of 5-HT<sub>3</sub> receptor antagonists not only to placebo but also to metoclopramide and other antiemetic drugs.

First generation 5-HT<sub>3</sub> receptor antagonists (ondansetron, granisetron, dolasetron and tropisetron) possess an equivalent safety and efficacy profile when used at equipotent doses (Aapro *et al.*, 2006:1442; Rojas & Slusher, 2015:905). The side effects of 5-HT<sub>3</sub> receptor antagonists are usually reported as being mild, with headache, constipation, diarrhoea and weakness (Feyer *et al.*, 2015). The pentameric 5-HT<sub>3</sub> receptor complex is a ligand-gated ion channel that mediates fast synaptic transmission in the brain (Brady *et al.*, 2007:1284).

Future formulations include an injectable subcutaneous long-acting formulation of granisetron, registered as APF530. It has been shown to maintain therapeutic drug levels of granisetron for at least five days. The slow and sustained release of granisetron can be used for the prevention of both acute and delayed CINV associated with MEC and HEC (Boccia *et al.*, 2016). This new formulation of granisetron (APF530) is currently in research and not yet licensed for use in South Africa (Navari & Rapoport, 2016:28).

The combination of dexamethasone and 5-HT<sub>3</sub> receptor antagonists remained the backbone of CINV prevention until recently, and this combination has been reported to lack effectiveness in preventing late onset CINV, with nausea specifically (dos Santos *et al.*, 2012:1281). The short half-life (approximately eight hours) makes it unsuitable for the effective prevention of delayed CINV (Boccia *et al.*, 2016). The suboptimal efficacy of 5-HT<sub>3</sub> receptor antagonist monotherapy, especially for delayed symptoms of nausea, is evident in reported trials (Aapro *et al.*, 2012:235; Bloechl-Daum *et al.*, 2006:4476).

### **2.6.2 Second generation serotonin receptor antagonists (palonosetron)**

In 2003, palonosetron was added to CINV guidelines (Burke *et al.*, 2011:131). Palonosetron is a novel, high potent and selective second generation 5-HT<sub>3</sub> receptor antagonist that has a strong receptor binding affinity and a long plasma elimination half-life (about forty hours). Palonosetron is approved for intravenous administration at a dose of 0.25mg, and is indicated for the prevention of CINV associated with MEC and HEC (Aapro *et al.*, 2006:1442; Boccia *et al.*, 2016). Several clinical studies found palonosetron to be effective in preventing both acute and

delayed CINV. Palonosetron's unique properties contribute to its advantages over other 5-HT<sub>3</sub> receptor antagonists in preventing delayed nausea.

Palonosetron differs in chemical structure from first generation 5-HT<sub>3</sub> receptor antagonists. The structural difference suggests palonosetron binds and acts differently at the receptor site relative to the other 5-HT<sub>3</sub> receptor antagonists (Grunberg *et al.*, 2013:6). Palonosetron exhibits allosteric binding; allosteric binding is when the drug binds elsewhere on the protein surface – other than the serotonin receptor – which creates a conformational change in the serotonin receptor, so that serotonin binding is indirectly inhibited (receptor internalisation) (Yang & Scott, 2009:2261). Receptor internalisation results in a persistent, long-lasting inhibition of the receptor function. In addition to alienating the serotonin to the 5-HT<sub>3</sub> receptors, allosteric binding also induces a conformational change that brings about an increased binding affinity between palonosetron and the 5-HT<sub>3</sub> receptor. This is called positive cooperability; when one palonosetron molecule binds to the receptor, it increases the affinity of this receptor for a second palonosetron molecule. The allosteric binding, together with receptor internalisation and positive cooperability, help explain the prolonged inhibition of receptor function, and therefore the long duration of protection against nausea (Feyer & Jordan, 2011:33; Rojas *et al.*, 2008:469; Smith *et al.*, 2012:91).

Allosteric binding contrasts with orthosteric binding of first generation 5-HT<sub>3</sub> receptor antagonist, which binds directly at the active receptor site directly (Nussinov & Tsai, 2012:1311). Since first generation 5-HT<sub>3</sub> receptor antagonists remain at the cell surface (no receptor internalisation), it is reasonable to assume these antagonists are washed away by high levels of serotonin (explaining the thirty-fold higher binding affinity of palonosetron for 5-HT<sub>3</sub> receptors (Navari & Rapoport, 2016:33; Rojas *et al.*, 2010:194).

The added use of dexamethasone with a single dose palonosetron significantly increases the effectiveness of CINV prophylaxis throughout the five-day post chemotherapy period. Single-dose palonosetron was as effective as ondansetron in preventing acute CINV following HEC, and with dexamethasone pre-treatment, its effectiveness was significantly increased over ondansetron throughout the 5-day post-chemotherapy period (Aapro *et al.*, 2006: 1441).

Evidence of crosstalk between the NK-1 receptors and the 5-HT<sub>3</sub> receptors exists (see sections 2.6.32.6.1 and 2.6.1). Palonosetron can suppress NK-1 receptor function (NK-1 receptors are associated with this delayed emesis). Palonosetron does not bind to NK-1 receptors, but, activity at the NK-1 receptor could influence the 5-HT<sub>3</sub> receptor and vice versa (Grunberg *et al.*, 2013:6).

### 2.6.3 Substance-P (neurokin-1)

The growing understanding of the role of substance-P in emesis led to the development of NK-1 receptor antagonists for the treatment of CINV (Burke *et al.*, 2011:132). The first NK-1 receptor antagonist, aprepitant, was approved in 2003, followed by fosaprepitant, netupitant and rolapitant, leading to a substantial improvement in prophylaxis for CINV (Rapoport, 2017). Neurokin-1 receptor antagonists improve control of CINV in the acute, delayed and overall phases for patients who receive HEC and MEC (dos Santos *et al.*, 2012:1291). The NK-1 mediated effect starts at approximately fifteen hours following chemotherapy infusion and continues into the delayed phase (Rapoport & Demetriou, 2013:84). They act by inhibiting substance-P in the emetic pathways in the central- and peripheral nervous system (Navari & Rapoport, 2016:35). Substance-P is associated with multiple processes and their receptors are widely expressed in various human systems. They are associated with depression, stress, anxiety and emesis. NK-1 receptors and Substance-P are present in brain regions involved in the vomiting reflex, as described in section 2.3.1 (Garcia-Recio & Gascon, 2015).

Neurokin-1 receptor antagonists are generally well tolerated. Aprepitant and fosaprepitant are metabolised by a group of enzymes in the liver known as cytochrome P450. Cytochrome P3A4 (CYP3A4) and cytochrome P2A6 (CYP2A6) are two of the main enzymes in this group. Some chemotherapy agents are also metabolised by CYP3A4, such as etoposide, taxanes, irinotecan, vinca alkaloids, anthracyclines and cyclophosphamide. When aprepitant or fosaprepitant are issued together with any of these chemotherapy agents, the chemotherapy can have an increase in bioavailability, as they compete for the same enzyme for metabolism (dos Santos *et al.*, 2012:1289). Other side effects include: skin rash, headaches and hiccups.

- **Aprepitant** is the most widely-used oral NK-1 receptor antagonist antiemetic agent and in 2003, it was approved as the first NK-1 receptor antagonist (Feyer & Jordan, 2011:31). It is typically administered as a single oral dose, one to two hours prior to infusion of chemotherapy or as three doses taken orally: 125mg before chemotherapy on day one, and 80 mg on days two and three. No significant difference was detected during studies between the single and three-day aprepitant dose groups (Rapoport & Demetriou, 2013:85). Aprepitant is a high selective substance-P antagonist that significantly improves the pharmacotherapy of acute and delayed HEC-induced nausea and vomiting through action in the brain stem region of the central nervous system (Bergstrom *et al.*, 2004:1007).
- **Fosaprepitant** is a prodrug of aprepitant that is administered intravenously. It is rapidly converted to the active aprepitant and exhibits a similar half-life to orally administered aprepitant. A large trial validated the equivalency of fosaprepitant, the intravenous

formulation, with oral aprepitant. This allows more convenient administration of the NK-1 receptor antagonist, particularly in patients who cannot accept or tolerate an oral formulation (Basch *et al.*, 2011:4189; Rapoport & Demetriou, 2013:85; Weinstein *et al.*, 2016:172).

- **Netupitant** is a high selective NK-1 receptor antagonist with a long half-life of approximately 90 hours. It is administered as a fixed oral combination, of netupitant/palonosetron, known as NEPA, with the distinct 5-HT<sub>3</sub> receptor antagonist palonosetron (PALO) (Navari & Aapro, 2016:1356). Netupitant/palonosetron combination was found to be a convenient single oral dose antiemetic targeting dual pathways, and high effective over multiple cycles of HEC/MEC, in the acute and delayed phases (Gralla *et al.*, 2014:1334). Netupitant/palonosetron offers a guideline-consistent CINV prophylaxis (GCCP) while targeting two critical pathways associated with emesis (Hesketh *et al.*, 2015).
- **Rolapitant** is a high selective NK-1 receptor antagonist with a half-life of approximately one hundred and eighty hours (Navari & Aapro, 2016:1356). It is the most recent NK-1 receptor antagonist to be approved, and it is licensed for the treatment of delayed CINV associated with initial and repeat courses of emetogenic chemotherapy, including, but not limited to, HEC (Rapoport, 2017). In a randomised trial, rolapitant provided superior CINV protection to patients receiving carboplatin-based chemotherapy in comparison with the control. These results support rolapitant use as part of the antiemetic regimen in carboplatin-treated patients (Hesketh *et al.*, 2016:2418). Rolapitant was also associated with greater rates of no significant nausea in a randomised trial for patients receiving HEC. This would suggest a benefit over current therapies, as nausea remains a clinically significant problem in these patients (Rapoport & Demetriou, 2013:85). Unlike other NK-1 receptor antagonists, rolapitant does not inhibit CYP3A4, but it does inhibit CYP2D6 and breast cancer resistance protein (BCRP) (discussed under section 2.5.3 'Substance-P'). It has however, been reported by Barbour *et al.*, (2017:1272) to be safe when administered as part of triple therapy with concomitant medicines containing CYP2D6 and BCRP, such as ondansetron, docetaxel and irinotecan.

The addition of rolapitant to standard antiemetic therapy, improved protection against CINV in phase-3 trials of patients receiving HEC or MEC, as well as the quality of life of these patients (Chasen *et al.*, 2017:85).

#### **2.6.4 Glucocorticoids**

Glucocorticoids (dexamethasone specifically) was reported effective for CINV over thirty years ago and is still recommended in the major international antiemetic guidelines (MASCC), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) (Chu *et al.*, 2014:49). The exact mechanism of action in CINV is not known, but it may involve a reduction in the synthesis of eicosanoids produced after chemotherapy infusions, participation in the release of endorphins and a modification in the capillary permeability of the chemoreceptor trigger zone (Herrstedt & Grunberg, 2009:57).

Methylprednisone and dexamethasone have been used safely and effectively as both monotherapy and in combination with other agents for the management of CINV for many years and have been described as appropriate agents for management of delayed CINV (Grunberg, 2007:234). Control of delayed nausea can be significantly improved for patients who receive dexamethasone on day two and day three after chemotherapy infusions (Gillmore *et al.*, 2014:70).

Corticosteroids improve the efficacy of all the 5-HT<sub>3</sub> receptor antagonists (Herrstedt *et al.*, 2011:17). Several controlled clinical trials provide support for the view that the combination of a corticosteroid with a 5-HT<sub>3</sub> receptor antagonist is more effective than monotherapy for CINV prophylaxis (Aapro *et al.*, 2012: 235).

In a survey designed to detect potential corticosteroid related toxic effects, moderate-to-severe side effects noted for patients receiving dexamethasone for prophylaxis against delayed CINV included insomnia, GI symptoms, agitation, increased appetite, weight gain, rash, depression on cessation of treatment, hiccups and oral candidiasis (Aapro *et al.*, 2006:1442).

Steroids are interesting antiemetic drugs because of their widespread availability, low cost and reported benefits (Feyer *et al.*, 2015). Dexamethasone is as effective for preventing acute and delayed CINV as 5-HT<sub>3</sub> receptor antagonist and NK-1 receptor antagonist, however, for patients with a high risk for emesis, a combination of drugs from these three groups is most beneficial (Chin *et al.*, 2014:49).

#### **2.6.5 Olanzapine**

Multiple reports proved the effect of GCCP in chemotherapy patients; however, there is no effective therapy toward CINV, which is resistant to standard antiemetics (Abe *et al.*, 2015). Olanzapine is an atypical antipsychotic. It is used for CINV refractory to standard antiemetic treatment (Hocking & Kichenadasse, 2014:1145). Olanzapine is an inhibitor of multiple

receptors, including: serotonergic 5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>, dopaminergic D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors, alpha-1 adrenergic receptors, histaminic H<sub>1</sub> receptors and multiple muscarinic receptors (Chiu *et al.*, 2016:2381). It's binding affinity to the receptors involved with nausea and emesis (D<sub>2</sub>, 5-HT<sub>2c</sub> and 5-HT<sub>3</sub> receptors), provides rationale for its efficacy in both the prevention and rescue of CINV (Navari *et al.*, 2011:186).

Olanzapine seems to be useful in the prophylaxis of delayed nausea, and for treatment of breakthrough and refractory CINV (Jordan *et al.*, 2015:1082; Roila *et al.*, 2016:124). Side effects of olanzapine are tolerable and mild, including: somnolence, postural hypotension, dizziness, fatigue and dyspepsia (Jordan *et al.*, 2015:1082). Efforts to prevent and treat CINV have been usually directed at blocking neurotransmitter receptors in the area postrema, which is a chemoreceptor trigger site for vomiting in response to emetic drugs. Dopamine, endorphin, serotonin and neurokin receptors are found in this area, and are targets for preventing and treating CINV (dos Santos *et al.*, 2012:1281).

## **2.7 Emetogenic potential of intravenous chemotherapy treatment and other risk factors**

All patients receiving chemotherapy are not at equal risk for developing CINV, (Aapro *et al.*, 2006;1442). Risk factors for developing CINV can be grouped into two categories: treatment-related and patient-related (Feyer & Jordan, 2011:30).

### **2.7.1 Emetogenic potential of chemotherapy agents**

The emetogenicity of chemotherapy refers to its capacity to induce nausea and vomiting when administered without adequate antiemetic prophylaxis and is the major known risk factor for CINV used as guidance for antiemetic treatment (Chu *et al.*, 2014:51). Chemotherapeutic agents were first classified by Hesketh according to their emetogenic potential in the absence of antiemetic prophylaxis (Boccia *et al.*, 2016). The current classification of the emetogenic potential for chemotherapy agents are stratified as follows: HEC with > 90% risk of inducing CINV, MEC with 30-90% risk, low emetogenic potential (LEC) with 10-30% risk and minimal emetogenic potential (< 10% risk), and can be viewed in Annexure H (Burke *et al.*, 2011:132; dos Santos *et al.*, 2012:1280).

Some agents are ranked as MEC when given as single agents, whereas, the combination seems to be as emetogenic as HEC agents. Agents at the upper end of the MEC classification shows an increased risk of emetogenic potential, as do chemotherapy regimens that extend beyond one day (Weinstein *et al.*, 2016:175). These agents are known as 'other MEC agents' and include carboplatin, oxaliplatin and irinotecan (Herrstedt *et al.*, 2011:16). More examples of 'other MEC agents' include oxaliplatin, doxorubicin and cyclophosphamide, as they have a

known potential for delayed emesis even though they are classified as MEC agents. Their potential to cause CINV is higher and additional antiemetic prophylaxis needs to be considered (see section 2.8) (Roila *et al.*, 2016:125).

One significant change for CINV was the reclassification of anthracycline-cyclophosphamide (AC)-based chemotherapy from the MEC category to the HEC category in 2011 (Rapoport, 2017). Guidelines from MASCC require determination of cyclophosphamide dose as mg/m<sup>2</sup> because doses  $\geq 1\ 500$  mg/m<sup>2</sup> are classified as HEC and doses  $< 1\ 500$  mg/m<sup>2</sup>, as MEC (Burke *et al.*, 2011:133).

Carboplatin (a second-generation platinum analogue) is classified as MEC; however, it has an emetic potential greater than that of many agents classified as MEC. Carboplatin is also associated with a risk of delayed emesis (Hesketh *et al.*, 2016:2419). For this reason, MASCC and the European Society of Medical Oncology (ESMO) guidelines were recently updated to recommend that CINV associated with carboplatin-based chemotherapy be treated in the same way as HEC (Rapoport, 2017).

Chemotherapy treatments considered as HEC include cisplatin, dacarbazine, mechlorethamine, streptozocin and cyclophosphamide ( $\geq 1500$  mg/m<sup>2</sup>); MEC includes a large number of agents including oxaliplatin, cyclophosphamide ( $< 1500$  mg/m<sup>2</sup>), cytarabine ( $> 1$  g/m<sup>2</sup>), doxorubicin, and related agents and irinotecan; LEC agents include methotrexate, mitomycin-C, paclitaxel, cetuximab, trastuzumab and others; and minimal agents are bleomycin, busulfan, vinblastine and others (Aapro *et al.*, 2012:234).

A course of chemotherapy is given in a regular schedule of cycles with periods of rest in between to allow the body to recover (National Cancer Institute). The number of treatment cycles may affect the risk of CINV, as well as the chemotherapy dose (Chasen *et al.*, 2017:86).

As mentioned, patient-related risk factors also influence the emetogenic potential of chemotherapy treatments and can push treatments into different categories (Hesketh *et al.*, 2016:2419).

### **2.7.2 Patient-related and other risk factors**

The risk of developing CINV is primarily related to the emetogenic potential of the chemotherapeutic regimen (see section 2.7), although all patients receiving chemotherapy are not at equal risk for developing CINV (Aapro *et al.*, 2006:1442).

Patient-related risk factors for CINV include: younger age and female gender (Waqar *et al.*, 2016:701). Women with a history of vomiting during pregnancy or of motion sickness, display a greater tendency for vomiting during chemotherapy. Male patients with a history of motion sickness will also have a higher risk of CINV (de Oliveira, 2015:118).

Other patient-related factors, which can favour emetic events are: weight (the higher the body mass index, the greater the risk of presenting with nausea and vomiting) and sporadic alcohol use (consumption of ten or less alcoholic drinks per week) (Ballatori & Roila, 2003).

Previous exposure to chemotherapy and the presence of CINV with prior chemotherapy can increase the risk of CINV in patients diagnosed with cancer, as well as the drug dose and the number of cycles undergone (Aapro *et al.*, 2006:1442). Previous experience has shown a decrease in the antiemetic effect during subsequent cycles (Bloechl-Daum *et al.*, 2006:4477).

Prevention of CINV from the start of chemotherapy is important, because delayed emesis is correlated with the presence of acute emesis and because patients who experience CINV in one cycle are more likely to develop anticipatory CINV during subsequent chemotherapy cycles (Aapro *et al.*, 2012:1987). Poor control of acute CINV is an established predictor for delayed CINV that typically peaks in severity between day two and day four, post-chemotherapy infusion (Aapro *et al.*, 2006:1442).

Additionally, disease-related features such as the primary site of the cancer, ECOG performance status of 1 and 2, histological subtype, clinical stage, presence of brain metastasis and presence of end-organ dysfunction may further impact the probability of emesis (dos Santos *et al.*, 2012:1280; Gillmore *et al.*, 2014:71).

Enhanced education and adherence to antiemetic guideline recommendations at the clinic play a role in successfully preventing CINV. The role of the oncology nurses and other healthcare providers are critical, and good patient-provider communication should be promoted. The involved patient has reduced intensity and distress of the CINV symptoms (Gillmore *et al.*, 2014:73; Wood *et al.*, 2011).

The emetogenic classification of chemotherapy drugs does not specifically include nausea (de Oliveira *et al.*, 2015:118). Nausea is a high individual experience, which is determined by: sex, racial-, psychological-, physiological- and neuroanatomical factors (Farmer *et al.*, 2015:1184). While continued research strives to attain the optimal antiemetic therapy, complete control of CINV, especially nausea, should be an optimistic goal for most patients receiving chemotherapy (Feyer & Jordan, 2011:36).

## **2.8 Current guidelines**

Guideline consistent CINV prophylaxis describes whether recommended drugs are administered or prescribed on recommended days for CINV prophylaxis. (Aapro *et al.*, 2012:1987; Boccia *et al.*, 2016). Consensus guidelines for antiemetic therapy are regularly updated by ASCO, ESMO with MASCC and NCCN (Gillmore *et al.*, 2014:68). The latest CINV guidelines are summarised in Annexure I.

### **2.8.1 General process of guidelines**

The antiemetic guidelines are evidence-based on well-conducted clinical trials and kept updated by expert panels consisting of key-opinion leaders with different specialities in the field. The panels keep the guidelines accurate through systematic reviews of the medical literature. They communicate regularly regarding any new information that might affect the guidelines. Comparator drugs/practices reviewed must be consistent with guidelines and best current practice. There should be an acceptable degree of benefit by the comparator, agreed upon by a majority of the panel, before the guidelines are amended. The detailed specifications of the different bodies are available on their independent websites (ASCO, 2017; MASCC, 2016; NCCN, 2018).

### **2.8.2 Chemotherapy is classified according to its emetogenicity**

The emetogenicity of chemotherapy agents is used as a framework for defining antiemetic treatment guidelines (Roila *et al.*, 2016:119). Section 2.7.1 discusses the four-level classification of intravenous chemotherapy in detail. Current antiemetic guidelines are similar with respect to the prevention of CINV after HEC, recommending triple therapy: a combination of a 5-HT<sub>3</sub> receptor antagonist, dexamethasone and a NK-1 receptor antagonist (see section 2.6.3). The prevention of CINV after MEC guidelines differ somewhat depending on the chemotherapy regimen, but a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone, (plus an NK-1 receptor antagonist for patients with additional risk factors (see section 2.7.2) is generally recommended (Abe *et al.*, 2015; NCCN, 2015; Rapoport & Demetriou, 2013:85).

### **2.8.3 Carboplatin is a separate group of moderate emetogenic chemotherapy**

Carboplatin forms part of the MEC agents, however, the broad range of expected emesis in the moderate level has posed an increasing challenge to efforts to provide a single recommendation for antiemetic treatment that is appropriate for the entire moderate category. Carboplatin is in the “upper end” of the current MEC emetogenicity classification and the emetogenic potential of carboplatin may be greater than previously thought (Roila *et al.*,

2016:125). It could, in fact, be classified as a separate emetic risk group within the MEC setting (Rapoport *et al.*, 2016:24; Waqar *et al.*, 2016:700). With carboplatin treatment, the recommendation is to administer the NK-1 -containing triplet, while the recommendation in MEC (other than carboplatin) remains a 5-HT<sub>3</sub> receptor antagonist, plus dexamethasone. The only organisation that currently recommends that an NK-1 receptor antagonist should be administered with carboplatin is MASCC/ESMO, while NCCN recommends that an NK-1 receptor antagonist regimen be considered for select patients receiving MEC agents (Hesketh *et al.*, 2016:2418; Jordan *et al.*, 2016:4618; Yahata *et al.*, 2016:497).

#### **2.8.4 Anthracycline/cyclophosphamide combinations are moderate emetogenic chemotherapy agents, regarded as high emetogenic chemotherapy**

Combination chemotherapy consisting of an anthracycline (doxorubicin or epirubicin) and cyclophosphamide is commonly used for the treatment of breast cancer, with or without other agents (Roila *et al.*, 2016:121). This combination was historically classified as MEC, but AC-based regimens were recently reclassified as HEC in the ASCO guidelines (Boccia *et al.*, 2016; Jordan *et al.*, 2014:200).

#### **2.8.5 Guidelines for delayed, breakthrough, refractory CINV**

Despite the inclusion of a NK-1 receptor antagonist in HEC patients, delayed CINV – particularly delayed nausea – is more difficult to manage than acute CINV (Hesketh *et al.*, 2016:2418; Moradian *et al.*, 2015:217). Adhering to the current antiemetic guideline, utilising olanzapine (as an adjunct to the antiemetic regimen) after HEC, could improve symptom control (Rha *et al.*, 2016:387). There is currently a lack of guidelines definitively supporting a specific agent for treating CINV when standard prophylaxis is ineffective (refractory/breakthrough CINV – see section 2.5). Although olanzapine has not yet been included in all GCCP, it has been proven efficacious in clinical trials and case reports for the prevention of CINV in the delayed phase, and for the treatment of breakthrough and refractory CINV (Chiu *et al.*, 2016:2381; Navari *et al.*, 2013:1661; Navari, 2014:184).

#### **2.8.6 Guidelines for anticipatory CINV**

The best approach to preventing anticipatory CINV (see section 1.1) may be the optimal management of CINV in previous cycles of chemotherapy and, if needed, current guidelines propose the use of psychological therapies or benzodiazepines as treatment options (Molassiotis *et al.*, 2016:988). The amnestic and anxiolytic properties of lorazepam may also help prevent anticipatory CINV (Garrett *et al.*, 2003:39).

### **2.8.7 New treatments in the guidelines**

The oral combination of netupitant and palonosetron (NEPA) plus dexamethasone is an additional treatment option during the delayed and overall periods following chemotherapy, showing high levels of nausea control (Bosnjak *et al.*, 2014). This convenient antiemetic combination offers GCCP by targeting two critical pathways associated with CINV in a single oral dose administered only once per treatment cycle (Hesketh *et al.*, 2015). In South Africa, NEPA is not yet registered for use.

### **2.8.8 Non-pharmacological treatments for CINV**

Non-pharmacological approaches for preventing or treating CINV can be applied along with the pharmacological approaches (Genc *et al.*, 2013:254). Ginger is often advocated as beneficial for CINV, but studies regarding the effect of ginger on CINV have yielded both positive and negative results (Arslan & Ozdemir, 2015; Lee & Oh, 2013:169). There are studies available suggesting the benefit of therapies like acupuncture and acupressure against nausea and vomiting, but the design inadequacies, small numbers and lack of dose finding studies limit the power and generalisability of most available studies (Molassiotis *et al.*, 2014:13; Ryan *et al.*, 2012:1480). Current evidence supports the need for more methodologically rigorous studies to determine whether non-pharmacological therapies like acupuncture are effective for CINV (Enblom *et al.*, 2012:1360; Rithirangsiroj *et al.*, 2015:86).

Cannabinoids may be a useful therapeutic option for people with CINV who respond poorly to commonly used antiemetic agents, however, unpleasant adverse effects may limit their widespread use. Currently, cannabis is not a primary means of treatment for CINV. Many published studies on the effect of cannabinoids in nausea and vomiting are outdated and more research is needed in all areas related to the therapeutic use of cannabis (Wilkie *et al.*, 2016:674). Methodological limitations of the current trials limit the conclusions, and further research reflecting current chemotherapy regimens and newer antiemetic drugs could likely modify the current conclusions (Smith, 2015).

### **2.8.9 The evidence-practice gap**

In a large prospective study, Aapro *et al.* (2012:1990) found that while guidelines for preventing CINV are widely available, clinical uptake of guidelines remains low and CINV remains a persistent problem for patients diagnosed with cancer. To prevent this so-called evidence-practice gap, guideline-based CINV protocols should be implemented in clinics (Iihara *et al.*, 2016:409). In addition to the guidelines, healthcare providers at the clinic should educate the

patients and their caregivers about CINV, and the need for continuing professional education based on good clinical practices should remain a priority (de Oliveira *et al.*, 2015:122).

## **2.9 Chapter Summary**

Despite clear international guidelines and much research on the prevention of CINV, nausea in particular still seems to have a negative impact on patients' daily living, with nausea reported to be a worse experience and more disabling than the act of vomiting itself (Chasen *et al.*, 2017:86; Jordan *et al.*, 2014:197; Kenward *et al.*, 2015:36).

Several issues continue to limit the effectiveness of chemotherapy-induced nausea prevention and management: the lack of an assessment tool for measuring the nausea experience, patients failing to report their nausea experience, limited understanding of the pathophysiology of nausea, limited use of antiemetic guidelines and clinicians failing to appreciate the impact of nausea in patient lives (Basch, 2010:865; Hesketh *et al.*, 2018:1152; Yu *et al.*, 2015:281).

Patients should not accept nausea to be an inevitable part of their cancer treatment and a more proactive approach should be taken in managing chemotherapy-induced nausea (Molasiattis *et al.*, 2007:157). Effective communication and educating the patient is a crucial part of managing CINV to optimise the patient experience (Garrett *et al.*, 2003:45; Kamen *et al.*, 2014:2).

A better understanding of the pathophysiology of nausea and new approaches to its treatment are required (Navari & Rapoport, 2016:84). Current developing of prediction tools to identify patients at risk can also contribute to a better management of chemotherapy-induced nausea (Dranitsaris *et al.*, 2017:1261).

## CHAPTER 3: RESULTS

### 3.1 Introduction

This chapter, as mentioned in the preface, contains the empirical study results. The results are presented in two manuscripts which are ready for submission. The title of the first manuscript is: “Measuring nausea, an underestimated clinical reality in patients receiving intravenous chemotherapy.” The title of the second manuscript is: “The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy.” Table 3-1 shows the correlation between the manuscripts, the different parts of the MAT tool and the objectives of the empirical study.

**Table 3-1: The objectives discussed in manuscript form with relevant measuring tools**

Objective	Manuscript	Relevant sections of the measuring tool: MAT
Collected data on the incidence and configuration/patterns of CINV during the first three cycles of a patient’s chemotherapy; in the acute phase, the delayed phase and the overall phase for each subject; as well as day 7 and day 10 after chemotherapy infusion, including anticipatory nausea before subsequent cycles (data will be collected for cycle 1, 2 and 3 of treatments)	“Measuring nausea, an underestimated clinical reality in patients receiving intravenous chemotherapy.”	The MAT is in the format of a diary. Patients completed it on day 1, 2, 3, 4, 5, 7 and 10 after chemotherapy infusion. The information completed every day was identical. The 24-hour VAS measured the time to incidence of nausea, the duration of nausea and the intensity of nausea. Incidents of vomiting were recorded with a ‘yes/no’ question.
Measured the time to nausea, the intensity of nausea and the duration of nausea after chemotherapy infusion	“Measuring nausea, an underestimated clinical reality in patients receiving intravenous chemotherapy.”	
Compared the incidence of nausea with the incidence of vomiting for all subjects	“The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy.”	
Documented the possible patient-related characteristics placing a patient more at risk of chemotherapy-induced nausea for each subject before initiation of treatment.	“The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy.”	Patient-related characteristics were documented on a patient-information sheet at the start of the patient’s treatment. This was recorded on a spreadsheet for analysis at the end of study.

### **3.2 Manuscript 1**

This section presents a manuscript titled: “Measuring nausea, an underestimated clinical reality in patients receiving intravenous chemotherapy.” The paper will be submitted to the journal *Current Problems in Cancer* as a research article. The article was prepared according to the specific instructions to authors for the journal and can be viewed at the following link: <https://www.journals.elsevier.com/current-problems-in-cancer>

# Measuring nausea, an underestimated clinical reality in patients receiving intravenous chemotherapy

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## Abbreviations

AC	doxorubicin/cyclophosphamide combination chemotherapy treatment
ASCO	American Society of Clinical Oncology
CINV	Chemotherapy Induced Nausea and Vomiting
ESMO	European Society for Medical Oncology
GCCP	Guideline Consistent CINV Prophylaxis
HEC	Highly Emetogenic Chemotherapy
LEC	Low emetogenic Chemotherapy
MASCC	Multinational Association of Supportive Care in Cancer
MEC	Moderate Emetogenic Chemotherapy
NCCN	National Comprehensive Cancer Network
PROM	Patient Report Outcome Measures
QoL	Quality of Life
VAS	Visual Analogue Scale

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- Dr E Fourie: Statistical analysis of data.

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## Abstract

### Background

Chemotherapy-induced nausea and vomiting is one of the more distressing events for oncology patients and it has now been established that nausea has a greater impact than vomiting on patients' quality of life. Nausea is defined as the unpleasant feeling causing the desire to vomit and can be accompanied by symptoms such as tachycardia, dizziness and weakness. There is a gap in the literature about studying the impact of nausea compared to the impact of vomiting in oncology patients, with little information on the incidence, the duration and the intensity of nausea experienced. As nausea is a subjective sensation, measuring nausea could include misinterpretations from third parties. A standardised tool to measure nausea in a valid and reliable way is needed to collect informative data in all phases of treatment for this debilitating adverse event.

### Methods

This was an observational prospective study in a private oncology centre in Johannesburg. One hundred patients were recruited over a seven-month period. Ethical approval was obtained before commencement of the study. All patients receiving intravenous chemotherapy were eligible to take part. Patient reported outcome measures (PROMs) with visual analogue scales (VAS) were used to document the patients' experience of nausea and vomiting. Patients documented information in the diaries on the incidence, duration and severity of nausea, during the acute phase (0-24 hours), the delayed phase (25-120 hours), day 7 and day 10 after infusion of chemotherapy with episodes of vomiting recorded as a secondary endpoint. The demographic and clinical variables of the subjects, as well as patient risk factors known to cause CINV, were tabulated and summarised using descriptive statistics.

### Results

Despite Guideline Consistent CINV Prophylaxes (GCCP), 57% of the patients still experienced nausea (with or without vomiting) – independently of the emetogenicity of chemotherapy received. Patients experiencing nausea without vomiting made up 35% of the population, with a mean intensity of 5.4

(VAS score/10). Patients experiencing nausea and vomiting were 24% of the population with nausea intensity  $\mu = 6.3$  (VAS score/10). The median time to the first incident of nausea experienced was 21 hours (1–93 hours) post chemotherapy infusion. Of the patients experiencing intermittent nausea, the mean duration was  $\mu = 3$  hours (median = 4 hours) and of all patients experiencing nausea, 49% of them experienced continuous nausea.

#### Conclusions

Valuable information was gained on the experience of nausea in patients receiving intravenous chemotherapy. The study illustrated the underestimation of nausea in cancer patients. This information is useful in better understanding and managing nausea as well as supplying a platform for much needed further research in this field.

Keywords: Chemotherapy-induced nausea, duration, incidence, intensity

## 1 Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a serious side effect experienced by patients receiving chemotherapy and has a significant impact on patients' quality of life (QoL) [1].

Despite Guideline Consistent CINV Prophylaxes (GCCP), the control of nausea remains an unmet need, as 5-HT<sub>3</sub> receptor antagonists alone fail to control delayed nausea and the NK-1 receptor antagonists have reported inconsistent results [2]. A general gap in the literature about CINV is the low consideration for studying the impact of nausea as compared to vomiting [3].

The side effect of nausea was ranked worse than fatigue, depression or the impact of chemotherapy on their family and may be present for up to seven days after chemotherapy dosing [4].

Nausea is a subjective sensation and if CINV assessments are entirely based on the healthcare providers' opinion, it might lack objectivity and precision [3]. The managing of delayed nausea in particular is challenged by the fact that it occurs after the patient has left the clinic and is not available for direct observation [5]. Tools have been available for many years to assist in monitoring CINV, reported in the acute and delayed phase of treatment, respectively. Unfortunately, none of these tools include nausea as a separate entity, in regard to the frequency, duration and severity thereof [6].

## 2 Materials and methods

### Study design

This prospective observational study enrolled 100 subjects over a seven-month period at a private oncology centre in Johannesburg, South Africa. All patients signed informed consent and regulatory approval was received by the Health Research Ethics through the Medicine Usage in South Africa (MUSA) at the North-West University (NWU), before the commencement of the study (NWU-00360-16-S1). The aim of the study was to establish the true incidence and patterns of nausea in the different phases (acute, delayed, late-delayed and anticipatory) experienced by patients after receiving intravenous chemotherapy. The study did not interfere with the patients' management and treatment of cancer (also management and treatment of CINV) in any way. Each patient was

treated for cancer according to evidence-based guidelines as per standard practice. Demographic information was collected on each patient (age, gender and ethnicity) as well as a clinical history (cancer type and stage, Eastern Cooperative Oncology Group [ECOG] score, previous chemotherapy treatments and comorbidities). Information on the treatment during the study was recorded (treatment regime, emetogenicity of treatment, cycles of treatment received, concomitant medication [proton pump inhibitors were specified to distinguish between gastroesophageal reflux which could be a differential diagnosis for CINV] and antiemetic prophylaxes received). Patients received GCCP with every treatment infusion according to the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) with the Multinational Association of Supportive Care in Cancer (MASCC), and the National Comprehensive Cancer network (NCCN) guidelines. If a patient experienced CINV despite the prophylactic antiemetics (breakthrough CINV), additional antiemetic treatment was prescribed (rescue medication) according to these guidelines. The study required patients to record their experience of nausea and vomiting in a patient diary (issued by the researcher) for the first three consecutive cycles of their chemotherapy treatment.

#### Participants

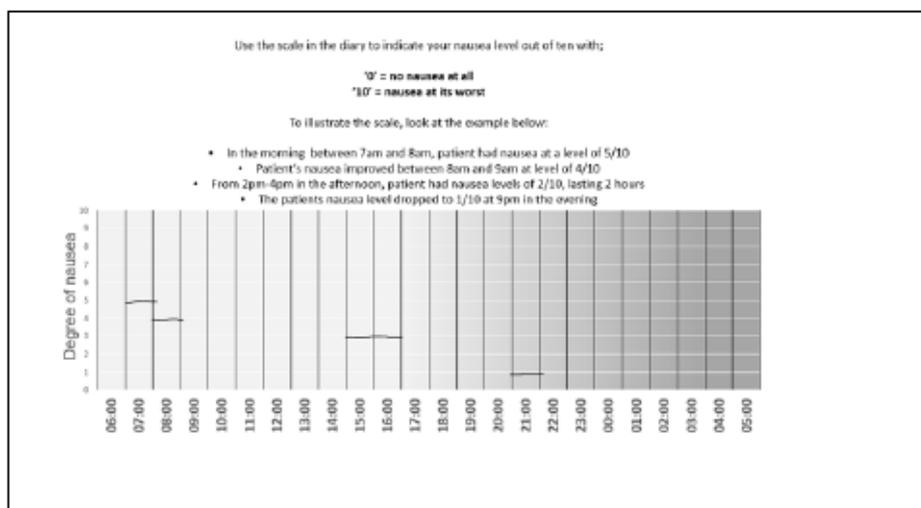
All patients receiving intravenous chemotherapy could take part in the study. Allowing all cancer types, stages of disease and ECOG scores to be part of the population, enabled the study to collect data that was true to the real-life experience of the patients. The only exclusion criteria were concomitant radiation therapy and surgery within two weeks of the study, as the impact of nausea on intravenous chemotherapy was the aim of the study. Patients willingly took part in the study after signing an informed consent document. Patients were informed on the management of CINV through prophylactic- and rescue antiemetic medication and were trained on how to use the patient diary.

#### Data collection tool

A Patient Reported Outcome Measure (PROM) with visual analogue scales (VAS) were used by each patient to report data on every incident of nausea. The measuring tool was based on the Multinational Association of Supportive Care in Cancer (MASCC) antiemesis tool (MAT) – with more

focus on the incidence, duration and intensity of nausea. Patients completed the diaries during the acute phase (0-24 hours) and the delayed phase (25-120 hours); and day 7 and day 10 after infusion of chemotherapy (late-delayed phase). The incidence of vomiting and the use of rescue medication were documented in the diaries as well as anticipatory nausea before subsequent cycles. An extract of the diary in Figure 1 shows the detailed information on nausea collected from the patients. A lot of information was gained on nausea regarding the time to the first event of nausea, the intensity of nausea and the duration of nausea, by drawing a single pencil line on the 24-hour grid in the patient diary.

Figure 1: An extract of the diary used with detailed information collected on nausea



### 3 Theory

Nausea has been described since the earliest times in Greek and Egyptian medical texts, and collections of diagnosis and remedies for nausea dating from before 1500 before Christ, can be found in the university library of Leipzig [7]. The sensation of nausea was frequently dismissed as merely a passing phenomenon until the early 1970's, after which substantial progress has been made in the prophylaxis and treatment of CINV [8]. These advances are reflected in the international clinical guidelines (ASCO, ESMO/MASCC, NCCN) for preventing CINV [4, 9, 10, 10]. Nausea is a

multidimensional experience with physical-, emotional- and psychological aspects [12]. The creation of nausea involves different systems: the central nervous system, the autonomic nervous system, the endocrine system and the gastrointestinal system [13]. The central pattern generator (CPG) in the brainstem receives and processes input signals from a variety of emetic stimuli from different parts of the body. Output signals are then returned from the CPG to different parts of the body, creating the phenomenon of nausea (looking pale, cold sweating, increased heart rate, respiratory arrhythmia and salivation) [14, 15,16].

The potential of chemotherapy treatment to cause CINV – in the absence of prophylactic anti-emetics – is known as the emetogenicity of the treatment [17]. The current classification of the emetogenic potential for chemotherapy agents are as follows: Highly emetogenic potential (HEC) with > 90% risk of inducing CINV, Moderate emetogenic potential (MEC) with > 30-90% risk, low emetogenic potential (LEC), with 10-30% risk and minimal emetogenic potential (< 10% risk) [18]. Chemotherapy's emetogenicity is the main cause of CINV, but specific patient risk factors can increase the likelihood of certain patients experiencing CINV, like younger age, female gender, history of motion sickness and a history of morning sickness. A history of excessive alcohol use decreases the risk of CINV [2, 19].

Chemotherapy induced nausea and vomiting typically presents in two phases over a five-day period, namely, the acute phase and the delayed phase. The acute phase occurs  $\leq$  24 hours after chemotherapy administration of CINV (primarily mediated by 5- hydroxytryptamine type 3 [5- HT<sub>3</sub>] receptor signalling), whereas the delayed phase occurs > 24-120 hours after chemotherapy administration (primarily mediated by neurokinin- 1 [NK- 1] receptor signalling) [20,21].

Current antiemetic guidelines recommend triple therapy for patients administered cisplatin, doxorubicin/cyclophosphamide combination (AC), carboplatin-based chemotherapy or any other HEC regimen (a combination of a 5-HT<sub>3</sub> receptor antagonist, dexamethasone and a NK-1 receptor antagonist). For the prevention of CINV after MEC, guidelines differ somewhat depending on the

chemotherapy regimen, but generally a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone (plus an NK-1 receptor antagonist for patients with additional risk factors) is recommended [22].

## 4 Results

One hundred patients were enrolled for this study. Ninety-five evaluable diaries were collected for cycle one, 87 diaries for cycle two and 79 for cycle three. Reasons for all patients not completing all three cycles of the study were disease progression, treatment stopped/changed, patients passed away, non-compliance or withdrawal of consent. The population included 72 Caucasian patients, 16 African patients and 7 Indian patients with a mean age of 57 years (25–84 years). Females made up 72% of the population. Patient with a variety of cancers, in different stages and with different performance status scores were included in this study, in order to represent a population as close to real-life as possible (Table 1). A patient clinical history was recorded for all patients (cancer, stage, performance status [PS] score, previous treatment, co-morbidities and concomitant medication – patients using proton-pump inhibitors were specified, as this could mask gastroesophageal reflux, a possible differential diagnosis for CINV).

Table 1: Cancer types, stages and performance status score included in the population

Cancer Type (n = 95)		Stage (n = 95)		Performance status (n = 95)	
Breast Cancer	47	I	4	0	59
NHL	7	II	26	1	29
Prostate Cancer	5	III	23	2	7
Lung cancer	6	IV	42		
Colon Cancer	11				
Other	19				

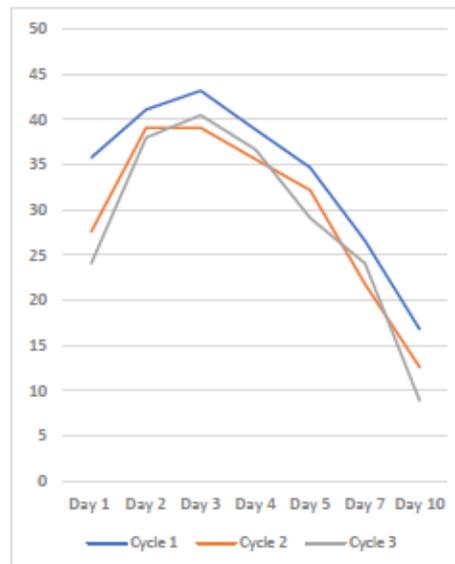
The only exclusion criteria were patients on concomitant radiation and/or surgery within two weeks of starting the study, as the aim of the study was the impact of nausea on intravenous chemotherapy. Every patient's treatment regime and antiemetic prophylaxes were documented, as well as additional antiemetic treatment (rescue medication) issued if patients experienced nausea and/or vomiting, regardless of the GCCP prescribed (breakthrough CINV). All possible patient risk factors that could impact the effect of CINV on study patients were documented (Table 2).

Table 2: Patient risk factors recorded

Patient characteristics/risk factors	Patient total
Age ≥ 60	42 (44.2%)
Age < 59	53 (55.8%)
Male	27 (28.4%)
Female	68 (71.6%)
No History of Motion Sickness	69 (72.6%)
☑History of Motion Sickness	26 (27.4%)
Alcohol Use in past 2 years:	
None	50 (52.6%)
<7 per week	40 (42.1%)
1-4 per day	5 (5.3%)
Emetogenicity	
LEC	25 (26.3%)
MEC	24 (25.3%)
HEC	46 (48.4%)
No Previous CINV	72 (75.8%)
☑Previous CINV	23 (24.2%)
No History of Morning sickness	38 (40.0%)
☑History of Morning Sickness	37 (38.9%)
Not applicable (male/female without pregnancies)	39 (41.1%)

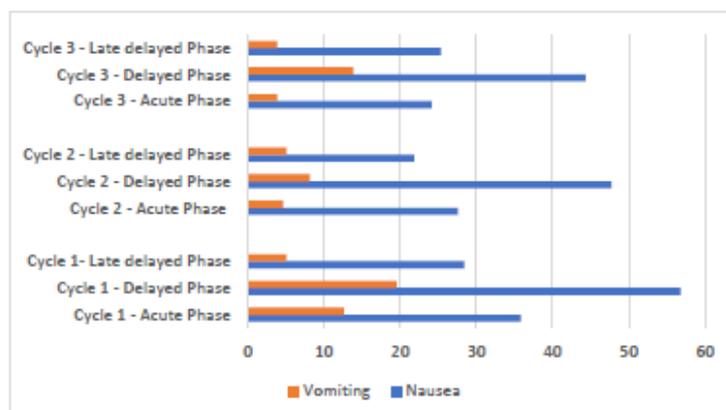
Despite GCCP, 57.9% of the patients still experienced nausea during cycle one of treatment, compared to only 24.2% of patients recording episodes of vomiting ( $p = 0.000$ ,  $\phi \sim 0.382$ ). This data was reflected in cycle two (50.2% patients with nausea and 13.8% patients with vomiting [ $p = 0.000$ ,  $\phi \sim 0.395$ ]) and cycle three (45.6% patients with nausea and 17.7% patients with vomiting [ $p = 0.000$ ,  $\phi \sim 0.507$ ]). There was a complete absence of vomiting in 27.3% and 38.9% of patients who recorded nausea during cycle two and three, respectively.

Figure 2: The incidence of nausea from day 2 to day 10 after chemotherapy infusion



Nausea was experienced by 58%, 51% and 46% of patients experienced nausea during the three consecutive cycles of treatment (Figure 2) Nausea experienced during the delayed phase seemed to be the more challenging phase for patients, as has been identified in published literature. Delayed nausea was experienced by 56.8%, 47.7% and 44.3% of all patient in the three subsequent cycles, compared to an incidence of acute nausea (35.8%, 27.6% and 24.1%). Nausea in the late-delayed phase (measured on day 7 and day 10) was reported less, compared to the acute and delayed phase, but indicated the incidence of nausea experienced by patients even ten days after chemotherapy infusion with 28.4%, 21.8% and 25.3% for the three cycles of treatment. A statistically significant association was found between the incidence of nausea and the incidence of vomiting (measured during the overall phase with  $p = 0.000$ ) in all three cycles, however, episodes of vomiting was recorded far less, as displayed in Figure 3 with acute phase vomiting recorded by only 12.6%, 4.6% and 3.8% of patients. As with nausea, the highest incidence of vomiting was recorded during the delayed phase (19.5%, 8.1% and 3.8% for cycle one, two and three, respectively).

Figure 3: The incidence of nausea compared to the incidence of vomiting as recorded in the acute, delayed and late-delayed phase of cycle one, two and three



Anticipatory nausea was recorded by 15.8% of patients, 24-hours before the infusion of the second chemotherapy treatment, with 21.8% and 19% patients reporting anticipatory nausea before commencing cycle three and four (a statistically significant association between overall nausea experienced in the previous treatment and anticipatory nausea in the following treatment and was found during all three cycles,  $p = 0.000$ ).

By using the expanded version of the MAT to record incidents of CINV (by the patients), the study managed to record detailed information on the intensity and duration of nausea (Table 3).

Table 3: Detailed information recorded on the incidence of nausea regarding the time to first event, the intensity and the duration for cycle one, two and three

	Cycle 1	Cycle 2	Cycle 3
Incidence of nausea (overall phase)	57.9%	50.6%	45.6%
Time to first event of nausea	28.52 hours	30.66 hours	28.21 hours
Intensity of nausea (VAS score out of 10)	5.88	5.97	5.85
Intermittent nausea – mean duration per episode (hours)	4.07	3.28	3.83
% Patients with continuous nausea	31.6%	21.8%	24.1%

Patients experiencing nausea during this study was between 46-58% of the population over the three cycles, with the highest mean intensity of 5.97 during cycle two (VAS score/10). The (mean) time to the first incident of nausea experienced for all cycles were at the start of the delayed phase ( $\mu = 28.52$  hours during cycle one). Of the patients experiencing intermittent nausea, the mean duration was between 3.28 hours and 4.07 hours per incident. Of all patients experiencing nausea, between 21.8% and 31.6% of them experienced continuous nausea.

## 5 Discussion

The study was conducted with a population well represented in many cancer types and in various stages of the disease. It was intended to collect data as close to the real-life experience of the patients as possible. This was further supported by using an expanded version of MAT, where detailed information on nausea could be collected in a user-friendly manner by the patients.

Data in published literature on the incidence of CINV was reflected by data recorded in this study.

Nausea is problematic for cancer patients receiving intravenous chemotherapy and was experienced by half of the patients taking part in this study. There was a significant association between the incidence of nausea and the incidence of vomiting in patients on the study, although vomiting was much more controlled during the acute phase, the delayed phase and the late-delayed phase. Only 24.2% of patients experienced vomiting during cycle one, with 13.8% and 17.7% during cycle two and three.

Despite strict adherence to GCCP and rescue medication issued as per current guidelines, nausea was a persistent problem for half of the population. The nausea experienced for the majority of the patients started in the delayed phase (day two after chemotherapy infusion) and was still experienced by day ten. Continuous nausea was experienced between 21.8% - 31.6% of the population, with no relief at any time during treatment received. The intensity of nausea varied between 0.5/10 and 10/10 on the VAS ( $\mu = 5.88$ ) for cycle one and this score was repeated for the following cycles.

Current antiemetic guidelines, including the latest new treatments, manage chemotherapy-induced vomiting for most patients. Despite strict adherence to guidelines for antiemetic prophylactic treatment and rescue medication, along with thorough patient guidance and communication, nausea was still experienced by half the study population, at medium to high intensity, for a duration of at least ten days after chemotherapy infusion.

## 6 Conclusions

Different approaches and/or medication need to be considered to manage nausea in cancer patients. Studies with nausea as primary endpoint, and valid and reliable measuring tools for nausea, can lead to information for better management of this adverse event. The impact of nausea on quality of life was not measured during this study but could be considered for further research.

## 7 Vitae

**Teresa Smit** is the responsible pharmacist at the Medical Oncology Centre of Rosebank. She received her oncology training at the NHS hospitals, Great Britain, 1999-2001, (University of Sunderland). Apart from pharmacy responsibilities she is involved in the Research Unit of the clinic with Investigator Initiated Studies. She is the project manager for local and international Investigator Initiated studies, liaising with sponsors and other partaking sites. She is currently completing a dissertation for a Magister Pharmaciae at the NWU, South-Africa

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**Dr Jesslee Du Plessis** is a general practitioner and senior lecturer at the North-West University (NWU) South Africa. She obtained her MBChB degree in 1999 at the University of Pretoria, and a master's degree (Cum laude) at NWU in 2011. She is actively involved in teaching and supervision of post-graduate students (NWU), as well as coordination and clinical evaluation of the exchange students both to and from the University of Wisconsin, Madison, USA. Through lecturing, conference presentations, written works (e.g., peer-reviewed original research, post-graduate student text)

clinical research, and involvement with professional societies, she seeks to improve the care of patients and the standard of student education.

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### **3.3 Manuscript 2**

Manuscript two, “The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy” will be submitted to *Annals of Palliative Medicine* as a research article and was prepared according to the author instruction of the journal that can be viewed at the following link: <http://apm.amegroups.com/public/system/apm/apm-instruction-for-authors.pdf>.

## APM – Annals of Palliative Medicine

### Title page

## The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy

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#### *Contributions:*

**Dr J Du Plessis & Ms I Kotze:** Supervision of concept and design of the study and manuscript, supervision in writing of literature review and manuscript, reviewing of the manuscript and poster presentation for academic content and approval of version to be published.

**Mrs M Cockeran:** Verification of the research design, guidance in the interpretation of the results.

**Dr E Fourie:** Statistical analysis of data.

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## The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy

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### Abstract

**Background:** The magnitude of the incidence and impact of nausea on patients receiving intravenous chemotherapy seems to be underestimated by healthcare professionals. Development of effective anti-emetic treatments has contributed to the resolution of chemotherapy induced nausea and vomiting (CINV). However, there is a concern that vomiting has been the initial focus of anti-emetic research and nausea was perceived as a secondary endpoint. Nausea's incidence and impact on patients' quality of life remains a major unmet medical need. Through focusing on the incidence of nausea independently of the incidence of vomiting, valuable information has been gained on this distressing side effect, including identifying patient risk factors contributing to the increased experience of nausea.

**Methods:** The study followed a prospective, observational study design in a private oncology centre in Johannesburg, South-Africa. Ethical approval was obtained before commencement of the study, followed by the recruitment of one hundred subjects over a seven-month period. Patient-reported outcome measures (PROMs) were used to measure nausea with an amended version of the Multinational Association of Supportive Care in Cancer antiemesis tool (MAT). Patients documented information in their diaries on the incidence, duration and severity of nausea, during the acute phase

incidence, duration and severity of nausea, during the acute phase (0-24 hours), the delayed phase (25-120 hours), day 7 and day 10 after infusion of chemotherapy with episodes of vomiting were recorded as a secondary endpoint. Patients completed diaries for the first three consecutive cycles of treatment. The demographic and clinical variables of the subjects, as well as patient risk factors known to cause CINV, were tabulated and summarised using descriptive statistics.

**Results:** The population consisted of 68 females and 27 males with a mean age of 57 years (25 – 84). The emetogenicity of chemotherapy regimens administered were well represented with 26.3% low emetogenic chemotherapy, 25.3% moderately emetogenic chemotherapy and 48.4% highly emetogenic chemotherapy. Despite all patients receiving guideline consistent CINV prophylaxis, nausea was still experienced by 57.9% patients during cycle one, 50.6% patients during cycle two and 45.6% patients during cycle three. The incidence of patients experiencing nausea (in the absence of vomiting) was 35% compared to 2% patients experiencing vomiting (in the absence of nausea). Patient characteristics with a known risk to impact CINV were documented and significant impact in this study were found in female gender, age < 60 years, history of motion sickness and history of morning sickness.

**Conclusions:** Guideline consistent CINV prophylaxes seem to have vomiting under control for most patients receiving intravenous chemotherapy. Nausea, however, still seems to be a persistent adverse event during treatment. Female gender, age < 60 years, history of motion sickness and history of morning sickness increases the risk of experiencing nausea. A different approach is needed to manage nausea in the clinic

setting, along with standardised tools to measure nausea specifically. More studies need to be done with nausea a primary endpoint to address this ongoing medical need.

**Key words:** CINV, intravenous chemotherapy, persistent nausea

## Introduction

Chemotherapy-induced nausea is now recognized as a specific clinical problem which is often not optimally treated (1). It remains the most important unmet medical need regarding chemotherapy-induced nausea and vomiting (CINV) (2). For many years, CINV has been regarded as a single entity (3). As one of the most serious treatment side effects in patients with cancer, CINV can significantly compromise patients' quality of life, but due to evidence-based research and guideline consistent CINV prophylaxis (GCCP), chemotherapy-induced vomiting can be prevented in the majority of patients (4, 5). Despite this, patients still experience nausea and its burden is often underestimated by the healthcare professionals (4, 6, 7).

Chemotherapy-induced nausea and vomiting presents in three phases. The acute phase occurs within 0-24 hours post-start of chemotherapy infusion, whereas the delayed phase occurs within 25-120 hours post-start of chemotherapy infusion (8). Delayed nausea is more difficult to manage than nausea in the acute phase, which occurs only after the patient has left the clinic (9). Anticipatory CINV is triggered in patients by taste, odour, sight and thoughts of anxiety due to a history of inadequate antiemetic prophylaxis in previous cycles; and occur before subsequent chemotherapy cycles (5).

Chemotherapy agents are classified into four different levels of emetogenicity: highly emetogenic chemotherapy (HEC) with > 90% risk of inducing CINV, medium emetogenic chemotherapy (MEC) with a 30-90% risk, low emetogenic potential (LEC) with a 10-30% risk and minimal emetogenic potential (< 10% risk) (10). Guidelines for prevention and treatment of CINV are based on this classification and consist of combinations of dexamethasone, 5-hydroxytryptamine (5-HT<sub>3</sub>) receptor antagonists and neurokinin-1 (NK-1) receptor antagonists (11). Several studies have shown effective CINV prophylactic activity with olanzapine, an antipsychotic agent (12). Chemotherapy-induced nausea is not life-threatening but has a vast

impact on the patient and their treatment (13). Nausea leads to anorexia, malnutrition, dehydration and anxiety towards chemotherapy (14). This collectively plays a role in the overall recovery period of the patient and adds to the economic burden of medical care (15). The sensory experience of nausea and the associated physiological changes involve bi-directional interactions between the central nervous system, the autonomic nervous system and the endocrine system (1). The complex event of nausea can be simplified to a three-step process:

- Input signals from a variety of emetic stimuli are sent from different parts of the body to the brain.
- The central pattern generator or vomiting centre receives and processes all these signals.
- Output signals are returned from the central pattern generator to different parts of the body (16).

The main areas involved in the receiving and processing of nausea and vomiting stimuli are the chemo trigger zone in the area postrema, the nucleus tractus solitarius and the central pattern generator in the reticular formation (17,18). From here, output signals return to different parts of the body to create the somatic and autonomic symptoms accompanying nausea: pallor, sweating, salivation, swallowing, gagging, smooth muscle contraction, cramps and tachycardia (19).

Certain patient characteristics are documented as having an impact on the experience of nausea and vomiting. The female gender, patients younger than 60 years, patients with a history of motion sickness and patients with a history of morning sickness have a higher risk of experiencing CINV. Patients having a history of excessive alcohol intake (> 4 glasses per day) during the past two years are less likely to experience CINV. The emetogenicity of the chemotherapy contributes to the experience of nausea as an external factor (22, 2). Despite

decades of research, nausea is still not clearly understood, and very little published literature is available on chemotherapy-induced nausea.

## Materials and Methods

This prospective, observational study included 100 patients over a seven-month period, in 2017, receiving intravenous chemotherapy at a private oncology centre in South Africa. Of these 100 subjects, 95 diaries were evaluable and used in the study. Each patient signed an informed consent document approved by The Health Research Ethics Committee of North-West University, South Africa (NWU-00360-16-S1) before commencing with the study. Chemo-naïve patients, as well as patients who have received prior chemotherapy, could take part. This broad inclusion of patients gave a review of 'real-life' experiences of patients.

The study used visual analogue scales (VAS) and PROMs to get data to resemble patients' experience as accurately as possible, and to ensure data were comparable between patients (19).

The tools used for collecting data were based on the Multinational Association of Supportive Care in Cancer (MASCC) antiemesis tool (MAT) and were validated and standardised tools that were easy to understand and relatively quick to complete (20). The MAT is relied upon for its low patient burden and patient-friendly properties and measures both acute and delayed nausea and vomiting (21).

This study focused on the incidence and patterns of nausea in particular. The exact same format for MAT was used, but data were collected on an extended 24-hour table, where the patients could indicate the incidence, duration and intensity of nausea with one pencil marking.

By collecting the data in this way, it was expected that the results be as close to the real-life experience as possible. The diaries were completed by the patients themselves, aided by the definition of nausea as 'the feeling that you might vomit' and vomiting as 'the expulsion of stomach contents'. Patients documented information in the diaries on the incidence; duration

and severity of nausea during the acute phase (0-24 hours) and the delayed phase (25-120 hours); and day 7 and day 10 after infusion of chemotherapy.

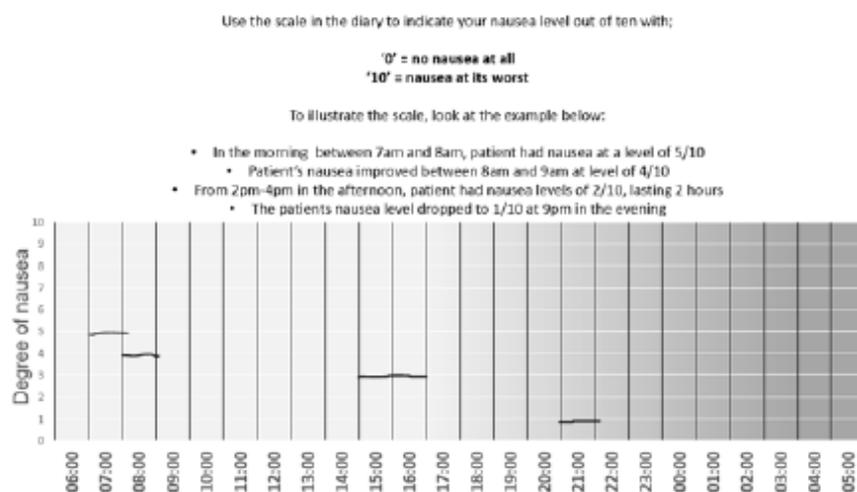


Figure 1: An extraction of the expanded version of MAT used by the patients to indicate detailed information on nausea experienced after receiving intravenous chemotherapy.

Anticipatory nausea before subsequent cycles was recorded, as well as the incidence of vomiting and rescue medication were documented in the diaries. The adapted MAT diaries used a VAS scale that represented 24 hours of the day for the seven days investigated to measure nausea with '0' being no nausea experienced at all, to '10' being nausea at its worst. On this scale, the patient marked exactly when nausea was experienced and its intensity (between 0-10).

Patients were requested to complete diaries for the first three consecutive cycles of their treatment. Ninety-five patients completed the diaries for cycle one, 87 patients completed cycle two and 79 patients completed diaries for three consecutive cycles. Reasons for some subjects not completing all three first consecutive cycles were disease progression, treatment stopped/changed, patients passed away, non-compliance or withdrawal of consent.

The patients captured their real-life experiences in the diary without any influence from the healthcare providers or clinic. Patients were issued with guideline consistent CINV prophylaxis (GCCP) and rescue medication was issued as per published CINV guidelines (22).

Patient demographics were recorded per patient before commencement of treatment, including known risk factors for CINV (age, gender, history of alcohol use in the past two years, history of previous CINV, history of motion sickness, history of morning sickness and the emetogenicity of the chemotherapy utilized).

Other data recorded were medication used to issue breakthrough nausea and/or vomiting (rescue medication), whether patients were issued with prescriptions for rescue medication to take out (TTO) (compared to patients only receiving prescriptions if they required rescue medication) and whether or not patients received proton-pump inhibitors (PPI) with chemotherapy treatment. These variables were tabulated and summarized using descriptive statistics.

## Results

### *The incidence of nausea compared to the incidence of vomiting*

One hundred subjects were enrolled over a seven-month period, of which 95 subjects' diaries were evaluable for cycle one (three patients passed away, one patient was non-compliant, one patient was not eligible after screening). The population consisted of 68 females (71.6%) and 27 males (28.4%) between the ages of 24 and 85 years ( $\mu = 57$ ). The ethnicity of the population was made up of seven Indian, 72 Caucasian and 16 African patients. Patients received a variety of chemotherapy treatments including different emetogenicity levels, consisting of 25 low emetogenic chemotherapy (LEC) patients (26.3%), 24 moderate emetogenic chemotherapy (MEC) (25.3%) patients and 46 highly emetogenic chemotherapy (HEC) (48.4%) patients. Patients with a variety of

cancers were treated, in different stages of disease and performance status scores – the study aimed to create as close as possible representation of real-life data (Table 1). The only exclusion criteria were concomitant radiation therapy and/or surgery within two weeks of chemotherapy treatment.

Table 1: All patients were included in this study to collect real-life data

Cancer type (n = 95)	
Breast Cancer	47
NHL	7
Prostate Cancer	5
Lung cancer	6
Colon Cancer	11
Other	19
Stage (n = 95)	
I	4
II	26
III	23
IV	42
Performance Status (n = 95)	
0	59
1	29
2	7

The incidence of nausea compared to the incidence of vomiting are captured in Table 2. In this study, 57.9% of patients experienced nausea, of which 61.8% of them was in the absence of vomiting - only 24.2% of the patients experienced episodes of vomiting in the overall phase during cycle one. A statistically significant association was found between the incidence of nausea and the incidence of vomiting (in the overall phase) in all three cycles, with  $p < 0.05$ . A practical medium effect was found for cycle one and two (with  $\phi \sim 0.382$  and  $\phi \sim 0.395$ ) and a practical large effect for cycle 3 ( $\phi \sim 0.507$ ).

Table 2: The incidence of nausea compared to the incidence of vomiting (overall phase) during cycle 1, 2 and 3.

The incidence of nausea compared to the incidence of vomiting for overall phase during cycle 1			
	No vomiting	✓ Vomiting	Total
No Nausea	38 (95.0%)	2 (5.0%)	40 (100%)
✓ Nausea	34 (61.8%)	21 (38.2%)	55 (100%)
Total	72 (75.8%)	23 (24.2%)	95 (100%)
The incidence of nausea compared to the incidence of vomiting for overall phase during cycle 2			
	No vomiting	✓ Vomiting	Total
No Nausea	43 (100.0%)	0 (0.0%)	43 (100%)
✓ Nausea	32 (72.7%)	12 (27.3%)	44 (100%)
Total	75 (86.2%)	12 (13.8%)	87 (100%)
The incidence of nausea compared to the incidence of vomiting for overall phase during cycle 3			
	No vomiting	✓ Vomiting	Total
No Nausea	43(100.0%)	0(0.0%)	43 (100%)
✓ Nausea	22 (61.1%)	14 (38.2%)	36 (100%)
Total	65 (82.3%)	14 (17.7%)	79 (100%)

The incidence of nausea experienced during cycle one was 35.8% in the acute phase and 56.8% in the delayed phase, 27.6% for the acute phase during cycle 2 with 47.7% in the delayed phase. Cycle three reflected this data with acute nausea recorded as 24.1% and delayed nausea 44.3%. Day 7 and day 10 were recorded as a 'late-delayed phase'. Nausea experienced during this time was less than nausea experienced during the overall phase, but still significant in 28.4%, 21.8% and 25.3% of the patients during the three consecutive cycles.

The mean time to the first incident of nausea was in the delayed phase for all cycles ( $\mu = 29.3$  hours). The intensity of nausea (mean) experienced on the VAS were 5.9 out of 10 for cycle one, 6.0 out of 10 for cycle two and 5.9 out of 10 for cycle three. Patients experiencing intermittent nausea had a mean duration of 4.1 hours, 3.3 hours and 3.8 hours per episode during cycle one, two and three respectively, with 25.8% of all patients experiencing nausea – experienced nausea continuously without relief during any cycle.

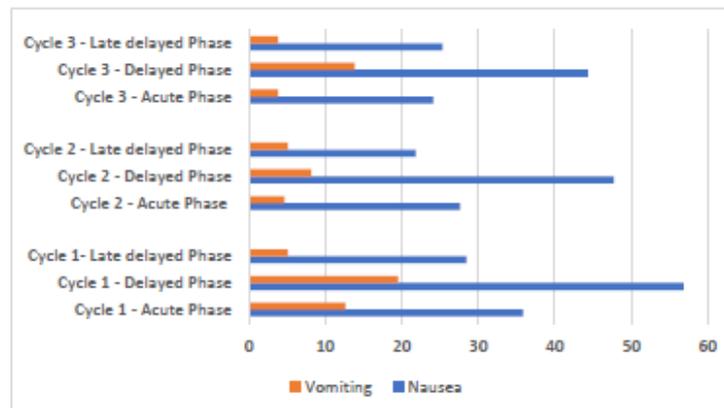


Figure 2: The association between the incidence of nausea and the incidence of vomiting for cycle 1, 2 and 3.

Vomiting seemed less of a problem during all three cycles, with only 12.6% patients reporting vomiting incidents during the acute phase for cycle one, 4.6% during cycle 2 and 3.8 % during cycle 3. The incidents of vomiting for the delayed phase was 19.5%, 8.1% and 13.8% for cycle one, two and three consecutively and during the late delayed phase only 5.1% (cycle one and two), and 3.8% (cycle three) of patients vomited. The delayed phase had the highest intensity of incidents reported for both nausea and vomiting.

#### Patient characteristics

Patient characteristics known to impact the incidence of nausea were recorded with the enrollment of every patient. Statistically significant impact was found with the history of morning sickness ( $p = 0.000$ ) the history of motion sickness ( $p = 0.002$ ), age  $\geq 60$  years ( $p = 0.016$ ) and gender of patients ( $p = 0.029$ ). The practical effect size of this impact was large for patients with a history of motion sickness and a history of morning sickness, and medium for female gender and age  $\geq 60$  years (see Figure 3).

Patients with a history of morning sickness had a 78.4% incidence of nausea with chemotherapy ( $p = 0.001$ ) and patients with a history of motion sickness showed an incidence of nausea of 80.8% ( $p = 0.006$ ). Female patients showed a 66.2% incidence of nausea

compared to only 37.0% incidence recorded in male patients ( $p = 0.009$ ). Younger patients (< 59 years) showed 70.4% nausea compared to patients  $\geq 60$  years with only 41.5% incidence of nausea ( $p = 0.005$ ).

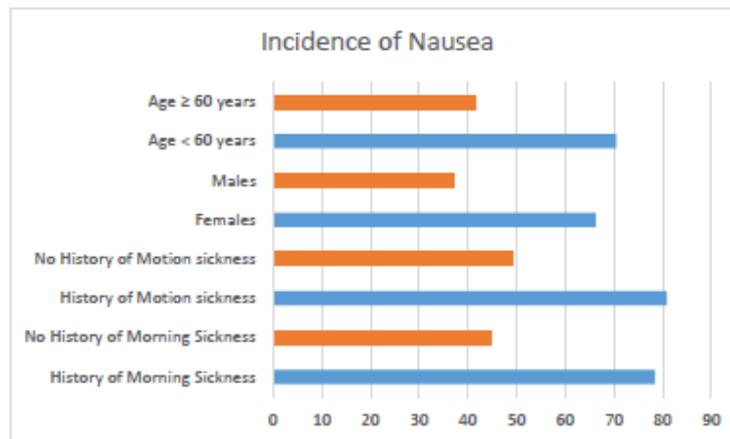


Figure 3: Patient risk-factors with a statistically significant impact on the incidence of nausea

The previous experience of CINV and a history of high alcohol use did not show a statistically significant impact on the incidence of nausea in this study. Patients experienced nausea independently of the emetogenicity of the chemotherapy administered, with LEC patients showing 40.0% nausea, MEC patients 62.5% nausea and 67.4% of all HEC patients experienced nausea.

## Discussion

The broad inclusion criteria of the study created a population with a variety in demographics, disease and treatment. The aim was to create a population as close to the real-life situation of cancer patients as possible. Patients completing their own diaries – indicating their experience of nausea and vomiting – recorded data that was valid and reliable, without misinterpretation from third parties. Data collected with the expanded MAT gave a wealth of information on the patients' experience of nausea and vomiting. Data collected for nausea specifically were

valuable - indicating a large part of the population experiencing significant intensities of nausea for hours at a time, with some patients having continuous nausea for the duration for their treatment (despite patients receiving GCCP and rescue medication).

A statistically significant association between nausea and vomiting was found in all three cycles, as well as an association between the emetogenicity of the treatment and nausea experienced. Despite this association, between 60-70% of all patients experiencing nausea (during all three cycles) did not report any vomiting incidents.

Patient risk factors impacting nausea reflected published data, showing an association between the experience of nausea and female gender, age < 60 years, the history of motion sickness and the history of morning sickness. This information can be used to identify high risk patients, approaching their treatment with strict following of GCCP, clear communication with the patient regarding the management of nausea and their experience of nausea. More studies are needed with nausea as primary endpoint, as well as a standardized tool to measure nausea in a valid and reliable way.

## Acknowledgements

- (1) Provision of study materials and patients: The Medical Oncology Centre of Rosebank, Johannesburg
- (2) Data analysis and interpretation: Marike Cockeran, Erika Fourie
- (3) Funding: none

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### 3.4 Presentation

An abstract was submitted to the annual SASMO conference which was held in Durban in November 2018. It was accepted as an oral presentation: “Risk factors associated with nausea in patients receiving guideline-based antiemetic prophylaxis with intravenous chemotherapy. A prospective, observational real-world study”.

#### 3.4.1 Slides

Slides used for the presentation of the data at the SASMO congress can be seen in this section. The cryptic notes below the slides were used by the presenter as presentation notes.

**NWU**® | *Medicine Usage in South Africa*

**Risk factors associated with nausea in patients receiving guideline-based antiemetic prophylaxis with intravenous chemotherapy. A prospective, observational, real world study.**

*T. Smit, J.M. Du Plessis, I. Kotze*

**SASMO CONGRESS 2018**  
16 - 18 NOVEMBER | DURBAN ICC  
MULTIDISCIPLINARY APPROACH TO CANCER CARE

Welcome & thank you

## The definition of nausea

MASCC 2004 "the feeling that you might vomit"



A strong feeling of disgust (Onions, 1973)

An unpleasant sensation (Stern, 2002)

A feeling of sickness with loathing of food (Onions, 1973)

Inclination to vomit (Ostler, 1962)

An unpleasant wavelike feeling in the back of the throat (NCI, 2009)

Detonating an unlocalizable sensation, a state of mind and pattern of behaviour – a turning away, from food, from everything, and a turning inwards. (Sacks 1981)

A rolling or uneasiness in the stomach (Spiegel, 1996)

 NWU\*

Many descriptions of nausea over millennia in literature. Examples of patients. Move onto how significant the feeling of nausea can be on daily living. Create awareness in audience.

## Introduction

- Vomiting can be prevented in the majority of patients – new drugs and current guidelines
- Despite guideline-based anti-emetic prophylaxis, 55-60% of patients still experience nausea
- To date perceived as secondary endpoint
- Limited information in literature, underestimated in practice

 NWU\*

CINV studied 2-3 decades. Literature most on vomiting (primary endpoint) Nausea & vomiting perceived as one. Not regarded as serious. Treating cancer > eliminating disease. CINV most feared AE. Development of effective antiemetic tx, relieve vomiting. Nausea not eliminated. Not life-threatening BUT QoL, underestimated → unmet medical need. Nausea still not clearly understood. This study focus – nausea. Valuable information gained.

## History of Nausea

*"T'is profitable for man that his stomach should nauseate or reject things that have a loathsome state of smell."*

~ Robert Boyle 1627-1691 ~

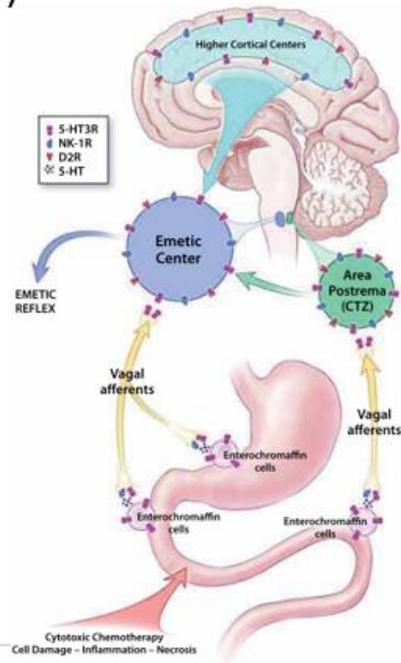
- 1500 BC
- Ancient Egyptian medicine: *The Papyrus Ebers*
- naus=ship asau = disgust
- Diverse range of diseases  
– 'protection'



Greek & Egyptian texts 1500 BC – University Leipzig. Collection of works describing nausea & remedies (papyrus). Body's way of protection. Understanding & development of Na changed over last millennium. Def difficult → many triggers, slow/sudden onset, prodromal symptoms vary. Greeks: asau + naus (sailing). Before 1970 – Na – seen as just a passing phenomenon.

# Pathophysiology

- Central Nervous System & Nucleus Tractus Solitarius
- Autonomic Nervous System
- Endocrine system



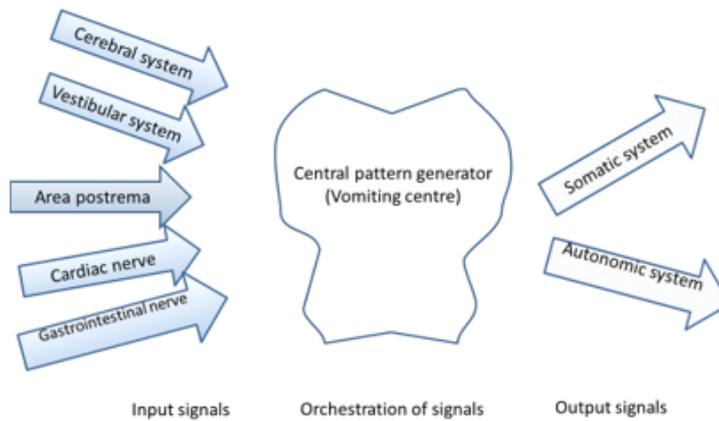
Grunberg, S. M., Slusher, B. & Rugo, H.S. 2013. Emerging treatments in chemotherapy-induced nausea and vomiting. *Clinical advances in hematology & oncology:H&O*, 11:1



Complex process of nausea – many neurotransmitters & receptors. CNS, ANS, endocrine. Simplified to 3 steps: Input signals, orchestration of signals in central pattern generator, output signals. Body interoceptive – perceive info & then make changes to restore balance. NTS – perceive & create feeling of nausea → corrective motor/sensory response. Thousands of synapses from all over body to all over diff brain regions. VC since 1891 – now CPG. Area that orchestrates events of n&v. CTZ not isolated by BBB – detect chemical agents. Diff threshold for diff people.

## Pathophysiology

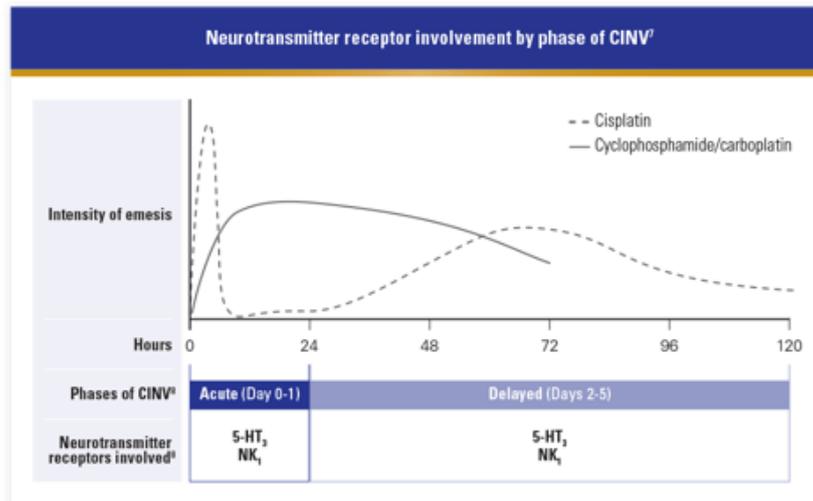
Multiple input signals from body processed in vomiting centre returning output signals to body



Hypothalamus – behaviour (pain, stress, fever). Olfactory – odours, vestibular – mid ear & balance, GI – ingested toxicities. Vomiting centre (now CPG) in brainstem. Output signals. Physical & Prodromal signs (pale, cold/sweat, salivation, ↑ heart rate, resp arryth, gagging, retch, cough, muscle contr (gut pain)).

## Levels of Emetogenicity

MEC  
HEC  
LEC



<https://www.cinvanti.com/advanced-nk1ra-formulation>



Physical changes – bi-phasal interaction in body. Groups – potential to cause nausea (with GCCP). HEC - > 90%. MEC 30–90%. Broad range. Specified guidelines depending on drug and risk factors. LEC – 10–30%. Guidelines developed to target different receptors, meds with different half-life.

# Pharmacology

1. First generation serotonin (5-hydroxytryptamine-3 (5-HT<sub>3</sub>))
2. Second generation serotonin (Palonosetron)
3. Substance-P (neurokinin-1)
4. Glucocorticoids
5. Olanzapine



Much progress – last 2 decades. 1980 – metoclopramide. 1990 – 5-HT<sub>3</sub> – cornerstone of CINV treatment. Acute phase only. 2003, NK-1. Increased selectivity. Half-life 40h. Receptors distributed all over body. Glucocorticoids – in combination. Olanzapine, refractory nausea, atypical anxiolytic. Receptors, 5-HT, D, M, H. Development of guidelines & GCCP. Nausea still taking a toll on pt

# Current Guidelines

**ASCO**  
Updated Oct 2017

**ESMO MASCC**  
Updated March 2016

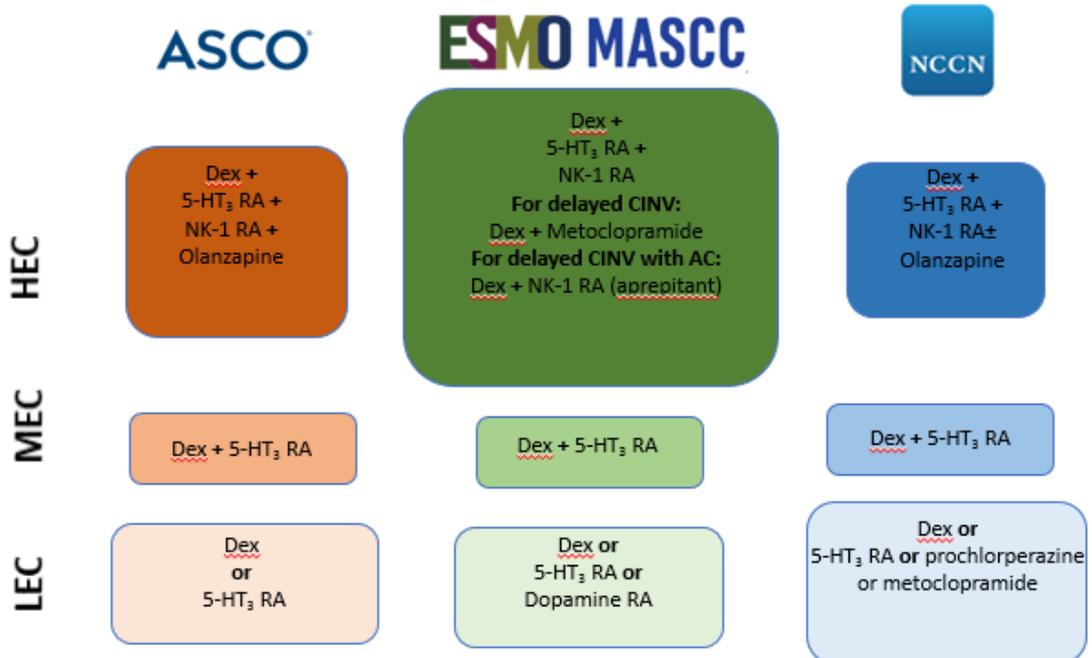
**NCCN**  
Updated June 2018

- General Process of Guidelines
- Carboplatin is a separate group
- AC are MEC agents regarded as HEC
- Delayed, Breakthrough, Refractory CINV
- Anticipatory CINV
- New treatments



Kept updated – key leaders/panels – reviewing data continuously.

# Current Guidelines



## Carboplatin and other MEC with high risk patients

ASCO®

ESMO MASCC

NCCN

Carboplatin area under the curve (AUC)  $\geq 4\text{mg/ml}$ :  
Dex +  
5-HT<sub>3</sub> RA +  
NK-1 RA

Dex +  
5-HT<sub>3</sub> RA +  
NK-1 RA

Dex + Palonosetron +  
Olanzapine  
or  
Dex + 5-HT<sub>3</sub> RA +  
Olanzapine

Treatment with oxaliplatin,  
cyclophosphamide or anthracycline:  
Add dexamethasone  
on day 2 + day 3

Patients with delayed CINV:  
Add dexamethasone  
on day 2 + day 3

Patients with additional risk factors:  
Dexamethasone +  
5-HT<sub>3</sub> Receptor Antagonist +  
NK-1 Receptor Antagonist



## Breakthrough & Anticipatory Nausea

ASCO®

ESMO MASCC

NCCN

Breakthrough

Olanzapine

Olanzapine

+ different drug class  
(olanzapine, benzodiazepine,  
cannabinoid, haloperidol,  
metoclopramide,  
phenothiazine, 5-HT<sub>3</sub> RA or  
Dex).

Anticipatory

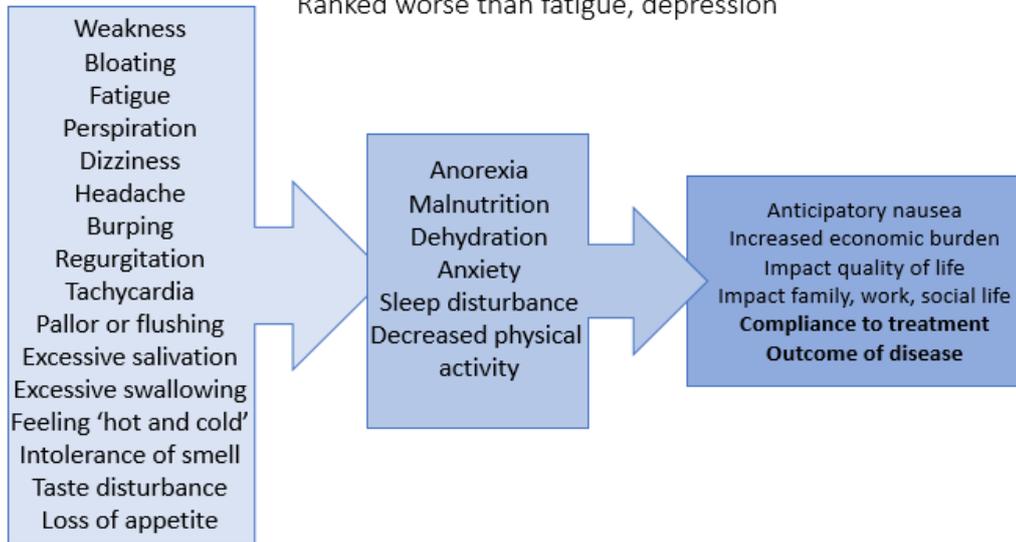
Emphasis on best possible  
control for acute and delayed  
CINV to prevent anticipatory  
CINV.  
Behavioural therapy with  
systematic desensitization

Emphasis on best possible  
control for acute and  
delayed CINV to prevent  
anticipatory CINV.  
Behavioural therapies (e.g.  
muscle relaxation,  
hypnosis)  
Benzodiazepines

Prevention is key, by using optimal  
antiemetic therapy during every  
cycle.  
Behavioural therapy, acupuncture,  
acupressure, anxiolytic therapy.

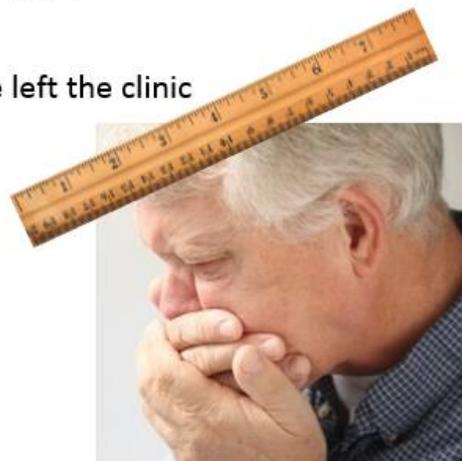
## The impact of nausea

Ranked worse than fatigue, depression



## The problem with nausea

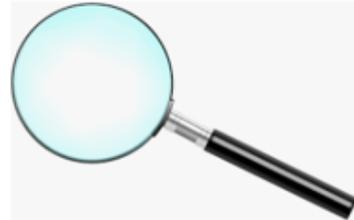
- Healthcare professionals underestimate nausea
- Delayed phase occurs after patients have left the clinic
- Perception, misinterpretation
- Inappropriate measuring tools
- Lack of suitable animal models



Subjective sensation. Animal models lack gag reflex.

## Aim of this study

- Establish the true incidence and patterns of nausea
- X 3 cycles
- Acute phase, delayed phase and overall phase
- Day 7 and day 10 after chemotherapy infusion
- Anticipatory nausea
- Measured: Time to nausea, Intensity of nausea, Duration of nausea
- Rescue anti-emetics
- Incidence of nausea vs incidence of vomiting
- Patient-related characteristics



## Tools to measure nausea

- Problem
- > 20 instruments exists to measure CINV - only one measured nausea in particular
- Self-reported instruments completed by the patients (PROMs)
- Subjective feeling
- Underestimated by third parties
- Design must be able valid and reliable
- Not add to burden of patient



MASCC Antiemesis Tool  
(MAT)

## MASCC Antiemesis Tool (MAT)

(extraction)

### **Nausea and Vomiting** **during the first 24 hours after chemotherapy:**

(This page refers to the first 24 hours following chemotherapy):

1) In the 24 hours since chemotherapy, did you have any **vomiting**? Yes  No

(Select one)

2) If you vomited in the 24 hours since chemotherapy, how many **times** did it happen?

(Write the number of times in this box)

3) In the 24 hours since chemotherapy, did you have any **nausea**?

Yes  No

(Select one)

4) If you had nausea, please circle or enter the number that most closely resembles your experience. How much nausea did you have in the last 24 hours?

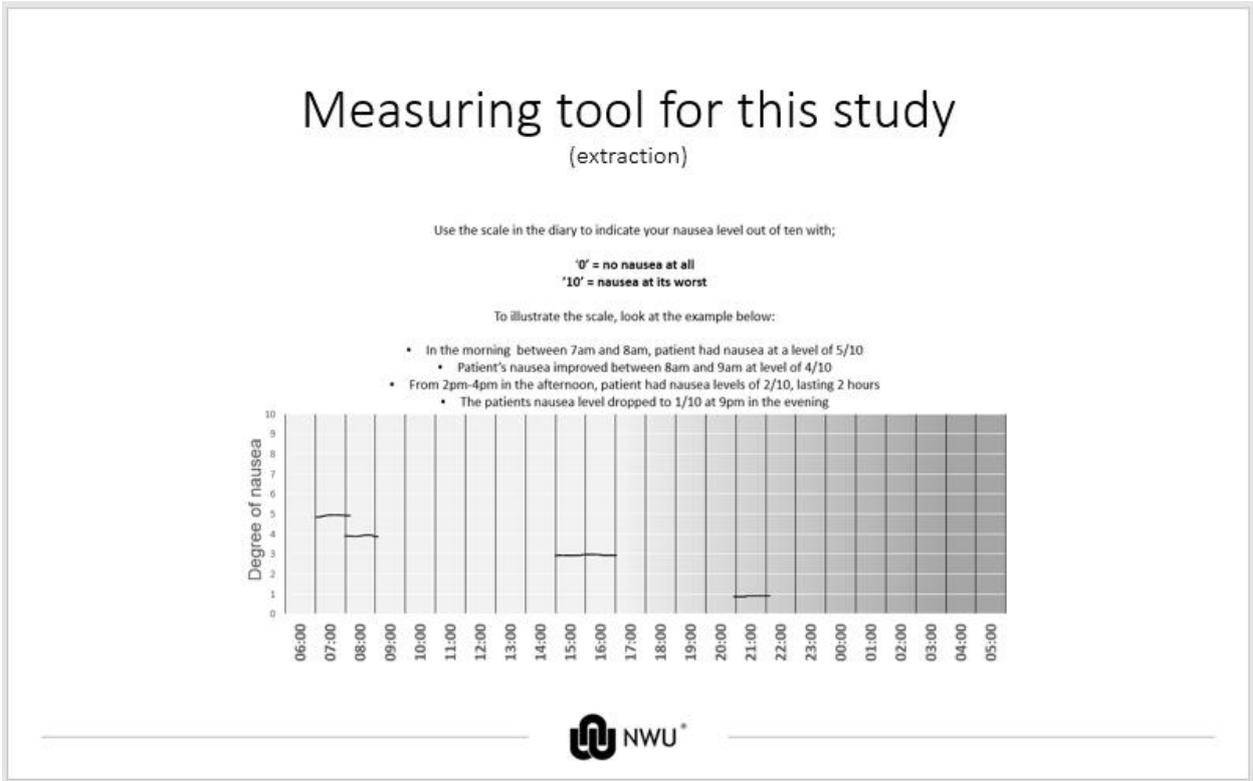
0 1 2 3 4 5 6 7 8 9 10  
None As much as possible

(Write the number in this box)

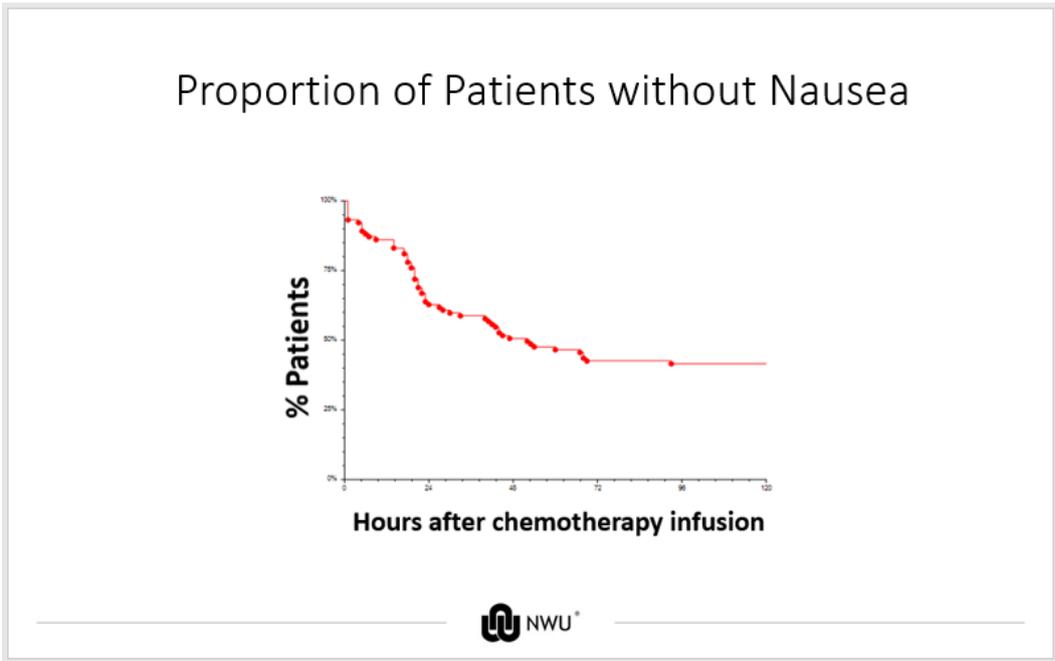
[https://www.mascc.org/assets/Guidelines-Tools/mat\\_english\\_questionnaire\\_2010\\_2.pdf](https://www.mascc.org/assets/Guidelines-Tools/mat_english_questionnaire_2010_2.pdf)



Meta-analysis > 20 tools, none measure nausea. MAT – user friendly, multilingual, valid & reliable. Still not much info on nausea.

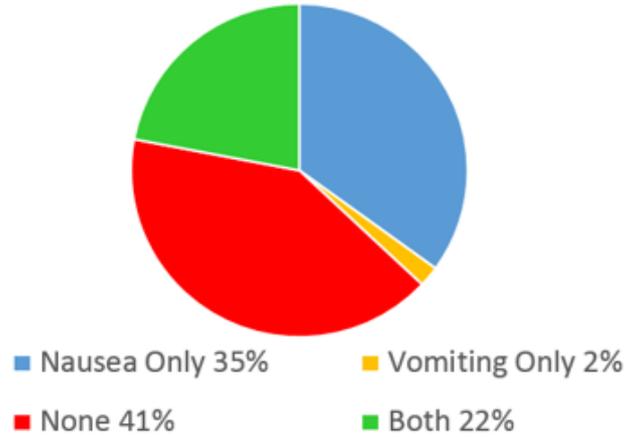


Expanded MAT. 24-hour grid. User friendly – one marking – incidence & duration & intensity. (Acute, delayed, anticipatory nausea. Day 7 & day 10) x 3 cycles.

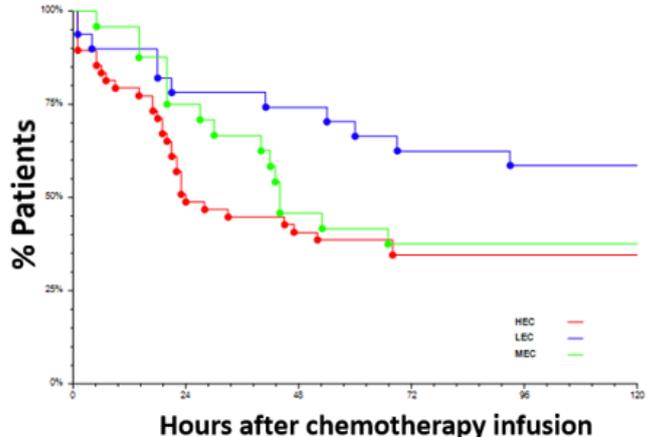


Observational study, GCCP prophylaxis. Document history & risk factors. Despite GCCP – > 50% patients nausea.

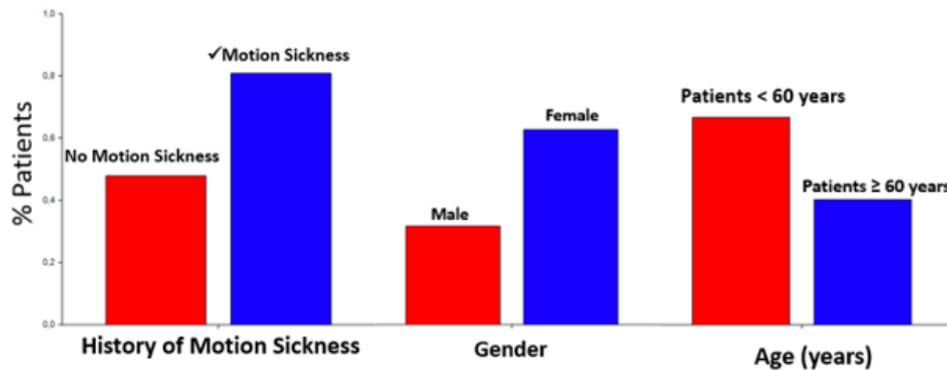
### Incidence of Nausea vs Incidence of Vomiting



### Impact of Emetogenicity on Nausea



## Impact of Significant Patient Risk Factors



## Conclusions

- Gender, age and motion sickness are significant risk factors associated with nausea independent of the level of emetogenicity of the chemotherapy utilized in patients receiving guideline-based antiemetic prophylactic treatment
- Nausea has to be approached different than vomiting in the clinic.
- Valid and standardised tool for nausea specifically
- Education and better communication between healthcare workers and patients to improve QoL while on treatment





### 3.5 Other data

Objectives not discussed in the manuscripts will be addressed in this section.

**Objective:** To determine the frequency of use of rescue antiemetics taken on days 1 through to 5 (0-120 hours), day 7 and day 10 after chemotherapy infusion.

#### 3.5.1 The use of rescue medication

All patients received antiemetic prophylactic treatment according to GCCP. Patients experiencing breakthrough CINV were issued prescriptions for rescue medication – also according to current guidelines.

Rescue medication was issued on either one of two time-points in the treatment process: Some patients (47.4%) received a prescription for rescue medication on day one, before the start of the first chemotherapy infusion. The patients could then have the prescription dispensed if or when they needed to. The other patients (52.6%) did not receive a prescription for rescue medication at the start of their treatment, but only when they needed medication for breakthrough CINV.

Rescue medication prescribed on the prophylactic prescriptions (at the start of treatment) was for oral ondansetron, 89% of the time. The other prescriptions were equally written for oral granisetron, metoclopramide, olanzapine, prochlorperazine or dimenhydrinate. Only 22.2% patients had their prescriptions filled to use as rescue medication in this group.

Prescriptions written at the time requested by the patient, were once again oral ondansetron (56%) – most of the time, followed by olanzapine (12%) and cyclizine (12%). The rest of the scripts were for granisetron, prochlorperazine, metoclopramide and clopamon. In contrast to the previous group, 56.0% of patients requested a prescription and used the medication for breakthrough nausea.

**Table 3-2: The frequency of use of rescue medication in different phases of treatment cycle 1.**

	Phase of treatment	Patients using rescue medication for breakthrough CINV		
		Cycle 1	Cycle 2	Cycle 3
<b>Acute Phase</b>	Day 1	28.4%	24.1%	27.8%
<b>Delayed Phase</b>	Day 2	27.4%	28.7%	30.4%
	Day 3	26.3%	33.3%	32.9%
	Day 4	22.1%	26.4%	26.6%
	Day 5	20.0%	20.7%	22.8%
<b>Late-delayed phase</b>	Day 7	11.6%	11.5%	12.7%
	Day 10	5.3%	4.6%	5.1%

Forty percent of the population did not use any rescue medication during the three cycles of the study. The patient percentage using rescue medication was stable during the different phases when comparing the three cycles of treatment.

**Objective:** Investigating the parallel between the prevalence of nausea after chemotherapy infusion and anticipatory nausea in subsequent cycles.

### 3.5.2 Anticipatory nausea

Anticipatory nausea occurred in 15.8% of patients 24-hours prior to cycle two and 21.8% of patients experienced anticipatory nausea prior to cycle three. The study showed that there was a statistically significant relationship between the incidence of nausea and anticipatory nausea in the subsequent cycle of treatment ( $p < 0.05$ ), as well as a practical significant association ( $\phi \sim 0.467$  and  $\phi \sim 0.464$ ).

This reflects data published in current literature and reiterates the importance of preventing CINV from the start of treatment to avoid increased risk of CINV in subsequent cycles of treatment.

### **3.6 Chapter summary**

This chapter discussed the findings of the objectives of the study. The manuscript: “Measuring nausea, an underestimated clinical reality in patients receiving intravenous chemotherapy” addressed the objectives of the incidence of nausea in all the different phases after receiving intravenous chemotherapy, as well as detailed information on the time to the first incident of nausea, the duration of nausea and the intensity of nausea. A wealth of information was gained by using an expanded version of MAT, documenting detailed information in a quick and user-friendly way.

The second manuscript: “The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy” compared the incidence of nausea with the incidence of vomiting in patient receiving intravenous chemotherapy. The article also discussed the possible risk factors associated with an increased risk of the incidence of CINV in patients diagnosed with cancer.

The frequency of the use of rescue medication was described as a separate section, along with the incidence of anticipatory nausea and if it is associated with the incidence of chemotherapy-induced nausea.

The researcher presented the study as a whole at the annual SASMO convention in Durban in November 2018. This was a 30-minute discussion to other oncology pharmacists and healthcare workers to give feedback on the study procedures and findings.

# CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

## 4.1 Introduction

Many decades of research have led to the development of a variety of CINV prophylactic medication and universal guidelines to maximise their benefit (Hesketh *et al.*, 2017:3240; Molassiotis *et al.*, 2017: 267). This brought relieve of vomiting for most patients receiving intravenous chemotherapy. Nausea, however, seems to be a persistent adverse event for these patients, specifically in the delayed phase after chemotherapy infusion (Jordan *et al.*, 2014:197).

The complicated pathophysiology of nausea in general is still not clearly understood. Nausea is a subjective sensation, complicating the measuring and interpretation thereof (Plevry, 2015:466). Chemotherapy-induced nausea is often underestimated by healthcare workers and as it is not life-threatening, it could get neglected in the care of the patient. Published literature and GCCP is largely focused on CINV as one entity (Rapoport *et al.*, 2015; Sommariva *et al.*, 2016:13). Not much information on chemotherapy-induced nausea is available.

This study’s aim was to collect information on the incidence of chemotherapy-induced nausea regarding the intensity and duration thereof in the different phases after chemotherapy infusions. It measured vomiting as a secondary endpoint, investigating whether an association between chemotherapy-induced nausea and chemotherapy-induced vomiting exists. Lastly it documented patient risk-factors that could impact the incidence of CINV.

## 4.2 Conclusion

The outcome to the aims and objectives of the study are discussed in this section.

Conceptualised CINV, its incidence, mechanism and prophylaxis from current evidence-based literature.

### 4.2.1 Literature objective 1

Chemotherapy-induced nausea and vomiting is a well-researched topic in oncology. The conducting of systematic literature searches delivered evidence-based research done on CINV over the last three decades, including the latest updates on new CINV medication and guidelines (section 2.8). The incidence of CINV is well documented in the literature. Most

research is done with vomiting as primary objective, and patients are documented as 'responders' to antiemetic prophylactic treatment if no vomiting incidents were recorded – regardless of the presence of nausea (Rha *et al.*, 2016: 4559).

Despite decades of research, the mechanism of CINV is still not clearly understood (Jordan *et al.*, 2015:1081). The mechanism of CINV is discussed in section 2.3 (Pathophysiology of nausea and vomiting). A general understanding of the receptors and neurotransmitters involved in CINV is found in the literature, but the literature did not distinguish between the mechanisms of nausea and the mechanism of vomiting.

The prophylaxis of CINV could be clearly described (see section 2.8), as GCCP guidelines are regularly updated by ASCO, NCCN and ESMO/MASCC.

Reviewed current literature regarding the mechanism of nausea specifically (related or unrelated to chemotherapy), to understand the incidence and impact thereof, as well as the possible patient characteristics expected with each.

#### **4.2.2 Literature objective 2**

A description of nausea and remedies thereof, have been studied since the earliest times and a literature search indicated documented data on nausea from 1 500BC (see section 2.2) (Stern *et al.*, 2011:4). Despite the continued study of nausea, a clear mechanism was not found in the literature search for it. The literature describes the mechanism of nausea and vomiting as one entity, and this is how it was described by the researcher (see section 2.3).

Very little published data on the incidence of chemotherapy-induced nausea was found in the literature. However, the impact of nausea on patients is clearly described in many journal articles. This was discussed in section 2.4.3.

Possible patient characteristics increasing the risk of experiencing CINV are well published in current literature. This important concept was described in section 2.7.2, as well as an article, 'The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy,' written for submission for publication to *Annals of Palliative Medicine*.

Collected data on the incidence and configuration/patterns of CINV during the first three cycles of a patient's chemotherapy; in the acute phase, the delayed phase and the overall phase for each subject; as well as day 7 and day 10 after chemotherapy infusion, including anticipatory nausea before subsequent cycles.

#### **4.2.3 Empirical objective 1**

The study recruited 100 subjects as per protocol. A complete data set could not be collected on all three cycles for various reasons: patients' disease progressed while on the study and treatment changed or stopped, one patient was recruited but was not eligible due to radiotherapy added to treatment, all patients were not compliant for all three cycles on the study. Due to the nature of cancer, a few passed away during treatment. As this was an observational study, the patient's treatment was not influenced in any way; for this reason, incomplete or missing patient diaries were lost for processing due to the above changes.

Cycle one produced 95 evaluable patient diaries, cycle two produced 87 evaluable diaries and cycle three produced 79 evaluable diaries. The diaries were completed on day 1–5, day 7, and day 10, as well as the day before the next cycle of chemotherapy infusion (Annexure C). The diaries produced clear data on the incidence of nausea in the different phases: the acute phase, the delayed phase, the late-delayed phase (day seven and day ten) as well as anticipatory nausea before subsequent cycles of chemotherapy.

The data collected is discussed in section 3.2. The data found in this study corresponds to the data in published literature on the incidence of CINV in different phases. However, it was the aim of this study to add more specific data on nausea, which cannot be found in current literature. The expanded MAT used was valuable to give very specific data on the incidence of nausea in the acute phase, delayed phase, the late delayed phase (day seven and day ten) and anticipatory nausea before subsequent cycles of treatment.

Measured the time to nausea, the intensity of nausea and the duration of nausea after chemotherapy infusion.

#### 4.2.4 Empirical objective 2

Most studies published on CINV have vomiting as a primary endpoint. Not much information exists on the incidence, duration and intensity of nausea experienced as an adverse event by chemotherapy patients. For this reason, an expanded version of the verified MAT was used to measure nausea in this study. To ensure that valid and reliable data were collected on patients' experience, a PROM was used with VAS – this was a user-friendly tool completed by the patients themselves (expanded version of the MAT – see section 1.7). A lot of information was gained on nausea regarding the time to the first event of nausea, the intensity of nausea and the duration of nausea, by drawing a single pencil line on the 24-hour grid in the patient diary.

The aim of this study was to get more information on nausea in this regard and is displayed in Table 4-1. To the researcher's knowledge – at the time this dissertation was written – no other published study has measured this information on nausea to compare with this study. This objective was discussed in the form of a manuscript "The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy" for submission as a research article in *Annals of Palliative Medicine* (Section 3.3).

**Table 4-1: The incidence, intensity and duration of nausea as collected from patient diaries in this study**

Cycle number		Cycle 1	Cycle 2	Cycle 3
Incidence of nausea (overall phase)		57.9%	50.6%	45.6%
Time to first event of nausea		28.52 hours	30.66 hours	28.21 hours
Intensity of nausea (VAS Score out of 10)		5.88	5.97	5.85
Duration of nausea	Intermittent nausea – mean duration per episode	4.07 hours	3.28 hours	3.83 hours
	Patients with continuous nausea	31.6%	21.8%	24.1%

Determined the frequency of use of rescue antiemetics taken on days 1 through 5 (0-120 hours), day 7 and day 10 after chemotherapy infusion.

#### **4.2.5 Empirical objective 3**

Any additional medication prescribed to patients for breakthrough CINV, over and above the GCCP, was documented and analysed. Not all patients on the study needed rescue medication, 40% of the population did not use any additional CINV medication at any time during the three cycles recorded. There was not a significant difference in the use of rescue medication between the three cycles of treatment. It was found that patients received medication in accordance with current published guidelines.

Investigated the parallel between the incidence of nausea after chemotherapy infusion and anticipatory nausea in subsequent cycles.

#### **4.2.6 Empirical objective 4**

Anticipatory nausea was recorded by the patients one day prior to cycle two as well as one day prior to cycle three. Our study showed there was a statistically significant relationship between the incidence of nausea and anticipatory nausea in the subsequent cycle of treatment ( $p < 0.05$ ) and was discussed in section 3.5.2.

The findings in this study reflect data published in current literature.

Compared the incidence of nausea with the incidence of vomiting for all subjects.

#### **4.2.7 Empirical objective 5**

Our study found a statistically significant association between the incidence of nausea with the incidence of vomiting in the overall phase of all three cycles with  $p < 0.05$ , with a practical medium effect for cycle one ( $\phi \sim 0.382$ ) and two ( $\phi \sim 0.395$ ), and a practical large effect for cycle three ( $\phi \sim 0.507$ ). This objective was discussed in manuscript form: “The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy” for submission for publication in *Annals of Palliative Medicine* (Section 3.3).

The results found in this study reflect published data in current literature, confirming a control of vomiting for most patients receiving intravenous chemotherapy, but no control for nausea in most patients. It also confirms the specific problematic area of the delayed phase for nausea in these patients.

Documented the possible patient-related characteristics placing a patient more at risk of chemotherapy-induced nausea for each subject before initiation of treatment.

#### **4.2.8 Empirical objective 6**

Patient risk factors were documented for each patient partaking in the study. These characteristics were analysed with the incidence of nausea in the patients at the end of the study. A statistically significant relationship was found between a history of motion sickness, a history of morning sickness, female gender and age  $< 60$  years and the incidence of nausea.

This agrees with literature published currently on patient risk factors for CINV. However, no significant association was found between emetogenicity, previous CINV or a history of excessive alcohol use and the incidence of nausea – as has been confirmed in literature. This could be due to too small population numbers for patient groups who have had previous chemotherapy treatment, as most patients on this study were chemo-naïve. There were very few patients with a history of excessive alcohol use, and this could lead to numbers that are not powerful enough for statistically significant outcomes as seen in the literature.

### **4.3 Recommendations**

Nausea must be approached differently to vomiting in the clinic. Studies with nausea as primary endpoint need to be conducted to get a better understanding of this persistent adverse event. A valid and standardised tool to measure nausea would assist in gaining a more detailed

information on nausea. Education and better communication between healthcare workers and patients to improve QoL while on treatment.

#### **4.4 Limitations**

Limitations to the study were an imbalance in the gender population, with only 27% males taking part in the study. The expanded version of the MAT used in this study was designed by the investigator, and although very useful information was collected with this tool, it could not be compared to any other studies. The diaries only available in English could have led to possible bias. The impact on the quality of life of the patients was not measured in this study and could be considered in future projects.

#### **4.5 Strengths**

The setup of the clinic allows the patients to have regular access to the research team; close communication between the patients and the research team encouraged good compliance and accuracy. With the inclusion criteria not being very restrictive, patients with a variety of cancer types and phases could be allowed on the study, allowing data to be collected on patients that would normally be excluded.

#### **4.6 Summary**

The impact of nausea on patients diagnosed with cancer and their carers was reiterated while conducting this study. Rightly so, the main focus of healthcare workers is to relieve the patient of their disease. In the process of this enormous task, adverse events like nausea might be overlooked.

The data collected was a realistic view on actual patient experiences, with nausea having a very large presence in the majority of patients on the study. The incidence of nausea experienced had a statistically significant association with the incidence of vomiting, but it was confirmed that vomiting is an adverse event that is far better controlled than nausea.

With very strict adherence to GCCP, the incidence of nausea was still experienced by half of the population, at a medium to high intensity, for hours at a time. Many patients on the study experienced nausea continuous without relief at any point during the treatment.

A different approach to nausea is needed in the clinics. A standardised measuring tool needs to be designed that can collect data on the subjective nature of nausea in a valid and reliable manner. Current guidelines might need adjustment to address nausea separately. More studies are needed to be done with nausea as a primary endpoint.



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## ANNEXURE A: INFORMED CONSENT PROCESS

  
THE CLINICAL ONCOLOGY RESEARCH PROGRAM  
CANCER CLINICAL TRIALS

<p>CONSULTING ROOMS AND CHEMOTHERAPY OUTPATIENTS CENTRE 173 GEFORD ROAD</p> 	<p>POSTAL ADDRESS</p> 	<p>COMMUNICATION</p> <p>PHONE : 27 11 880- FAX : 27 11 880- EMAIL :</p>
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DIRECTOR AND PHYSICIAN IN CHARGE  
DR BERNARDO L. RAPOPORT  
M.D. M.MED. (INT.MED.) (WITS)  
SPECIALIST PHYSICIAN, MEDICAL ONCOLOGIST

**SOP for obtaining informed consent.**

**Objective:** to describe the procedure for obtaining informed consent from a study patient to ensure that all patients are fully informed and fully understand the document he/she is signing.

**Responsibility:** Dr BL Rapoport

**Effective Date:** 1 September 2014

**Initiated by:** Dr BL Rapoport

**Checked by:** Teresa Smit *TSmit*

**Authorized by:** Dr BL Rapoport

Version 3 Page no 1 of 2

Supersedes all previous versions



[Redacted]

**THE CLINICAL ONCOLOGY RESEARCH PROGRAM  
CANCER CLINICAL TRIALS**

<p><b>CONSULTING ROOMS AND CHEMOTHERAPY OUTPATIENTS CENTRE</b></p> <p>[Redacted]</p>	<p><b>POSTAL ADDRESS</b></p> <p>[Redacted]</p>	<p><b>COMMUNICATION</b></p> <p>PHONE FAX E-MAIL</p> <p>[Redacted]</p>
<p><b>DIRECTOR AND PHYSICIAN IN CHARGE DR BERNARDO L. RAPOPORT M.D. M.MED. (INT.MED.) (WITS) SPECIALIST PHYSICIAN, MEDICAL ONCOLOGIST</b></p>		<p>[Redacted]</p>

**SOP for obtaining informed consent.**

Obtaining IC takes place in the PI's office, with only the PI, the clinic nurse and the patient with family / friend present.

When a treatment decision needs to be made, all treatment options are explained to the patient and family/friend. As part of this, the opportunity to take part in a research protocol is also offered to the patient. At this stage the PI requests the SC to bring an IC and to remain in the office and take part in the further explanation and discussion of the study to the patient and family/friend.

The design and purpose of the study, with all the experimental/ research and standard / routine treatments and study procedures are explained. The concept of randomization is also explained, if applicable. Furthermore the possible side effects, risks, benefits, confidentiality, costs and duration of the treatment and the study are discussed. Throughout, the patient has ample time to ask questions and an interactive discussion takes place. All questions are answered and patient is requested to take the IC home and to read carefully.

A return appointment is made, once the patient has decided to either take part or not. More discussions follow and the patient's concerns and questions are again addressed and answered. Once the patient is satisfied, the IC gets

signed and dated by the patient, the PI and a witness, in most cases the family/friend of the patient. A copy of the IC is given to the patient and the original IC is filed in the patient CRF. The IC process is documented in the source notes. The study specific procedures are now scheduled for as soon as possible.

Should there be an updated version of the Informed Consent, the same procedure as above is followed at the next visit.

## ANNEXURE B: INFORMED CONSENT FORM FOR STUDY



### **INFORMED CONSENT DOCUMENTATION FOR PATIENTS RECEIVING INTRAVENOUS CHEMOTHERAPY AT THE MEDICAL ONCOLOGY CENTRE OF ROSEBANK**

**TITLE OF THE RESEARCH STUDY:** The prevalence and configuration of nausea in patients receiving intravenous chemotherapy in a private oncology centre in South Africa

**ETHICS REFERENCE NUMBERS:**

**PRINCIPAL INVESTIGATOR:** Teresa Smit

**POST GRADUATE STUDENT:** Teresa Smit

**ADDRESS:** 129 Oxford Road, Corner Northwold Road, Saxonwold, 2196

**CONTACT NUMBER:** 011 880 4222/3

You are being invited to take part in a **research study** that forms part of my Master of Pharmacy in Pharmacy Practice. Please take some time to read the information presented here, which will explain the details of this study. Please ask the researcher or person explaining the research to you any questions about any part of this study that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research is about and how you might be involved. Also, your participation is **entirely voluntary** and you are free to say no to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part now.

This study has been approved by the **Health Research Ethics Committee of the Faculty of Health Sciences of the North-West University (NWU-00360-16-S1)** and

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will be conducted according to the ethical guidelines and principles of Ethics in Health Research: Principles, Processes and Structures (DoH, 2015) and other international ethical guidelines applicable to this study. It might be necessary for the research ethics committee members or other relevant people to inspect the research records.

#### **What is this research study all about?**

- This study will be conducted at The Medical Oncology Centre of Rosebank. Patients receiving intravenous chemotherapy will have the option to take part in this study investigating the prevalence of nausea in these patients. The study will involve questionnaires to be completed at home during the week of treatment. The study will involve the first three cycles of your treatment. The study will be done with experienced health researchers trained in clinical trial co-ordination and oncology pharmacy. One hundred participants will be included in this study.
- The researcher plans to investigate the prevalence, intensity and duration of nausea in patients receiving intravenous chemotherapy and to establish if there are certain patient characteristics placing a patient more at risk to chemotherapy induced nausea.
- The researcher also plans to compare the prevalence of nausea with the prevalence of vomiting. This information might lead to better control of nausea in patients receiving chemotherapy.

#### **Why have you been invited to participate?**

- You have been invited to be part of this research because you will be receiving intravenous chemotherapy at the Medical Oncology Centre of Rosebank.
- You also fit the research because you willingly sign informed consent for this study, you are 18 years or older and do not need to spend more than 50 % of your day in bed to rest due to the cancer or other diseases. Any patient receiving intravenous chemotherapy and take part in this study will receive the standard anti-nausea treatment that is given routinely to all patients in the practice.
- You will not be able to take part in this research if you have a history of severe vomiting during previous chemotherapy treatment, if you are taking any medication with anti-nausea properties, if you need palliative surgery or radiation therapy before or with the chemotherapy, or if you have active brain metastasis. Patient having nausea or vomiting 24 hours before the start of treatment will also be excluded.

#### **What will be expected of you?**

- You will be expected to complete a patient diary at home for the first 5 days after receiving chemotherapy. This will be completed after every cycle of treatment received, for the first three cycles. The diary will collect information on the incidence, duration and intensity of nausea you experience daily after chemotherapy treatment as well as incidence of vomiting for five days. You will record any medication you needed for nausea and vomiting in this time. The diary is easy to use and it will only take 5 minutes of your day. You will be expected to return the diary after every completed cycle at your next visit to the clinic

#### **Will you gain anything from taking part in this research?**

- There will be no direct gains for you if you take part in this study, as you will receive the standard preventative medication as all other patients at this clinic.

- The gain of the study is for better understanding of chemotherapy induced nausea, to better manage this dreaded side effect in patients in future.

**Are there risks involved in you taking part in this research and what will be done to prevent them?**

- There are no risks taking part in this study. The treatment you receive will in no way be altered or different due to participation. The visits to the clinic and all other routine consultations or tests will happen as it normally does without interference. There is a slight inconvenience of completing the diary at home and remembering to bring it along to clinic visits. Should you wish to not continue with completion of the diaries for whatever reason, you will be able to stop participation in this study at any time.
- There are more gains for you in joining this study than there are risks.

**How will we protect your confidentiality and who will see your findings?**

- Anonymity of your findings will be protected by using participant numbers. No personal details will be used to identify any patient. Your privacy will be respected by having all discussions in a private office. Your clinical file will be kept in cabinets in reception with restricted access for clinic personnel only. The data retrieved from the diaries will be captured on a password protected computer for storage and analysis by the researcher. Reporting of findings will be anonymous by only referring to the patients by number. Your results will be kept confidential by the researcher by not discussing it with anyone other than the oncologist. Only the researcher and oncologist will be able to look at your findings. Findings will be kept safe by locking hard copies in locked cupboards in the researcher's office and for electronic data it will be password protected. (As soon as data has been transcribed it will be deleted from the researcher's computer). Data will be stored for seven years.

**What will happen with the findings or samples?**

- The findings of this study could be used in future. Data will be analysed after completion of the study. Two articles will be written and published in relevant journals to report the outcome and recommendation of the research.

**How will you know about the results of this research?**

- We will give you the results of this research on request, once all data has been analysed for publication.
- You will be informed of any new relevant findings by contacting the clinic via email at [pharmacist@rapoport.co.za](mailto:pharmacist@rapoport.co.za).

**Will you be paid to take part in this study and are there any costs for you?**

This study is not funded. You will not be paid to take part in the study because your treatment involved at the clinic will not be altered in any way due to the study. There will thus be no costs involved for you, if you do take part in this study. Refreshments will be available in the clinic.

**Is there anything else that you should know or do?**

- You can contact Teresa Smit at 011 880 4222/3 if you have any further questions or have any problems.
- You can also contact the Health Research Ethics Committee via Mrs Carolien van Zyl at 018 299 1206 or [carolien.vanzyl@nwu.ac.za](mailto:carolien.vanzyl@nwu.ac.za) if you have any



concerns that were not answered about the research or if you have complaints about the research.

- You will receive a copy of this information and consent form for your own purposes.

By signing below, I ..... agree to take part in the research study titled "The prevalence and configuration of nausea in patients receiving intravenous chemotherapy in a private oncology centre in South Africa".

I declare that:

- I have read this information/it was explained to me by a trusted person in a language with which I am fluent and comfortable.
- The research was clearly explained to me.
- I have had a chance to ask questions to both the person getting the consent from me, as well as the researcher and all my questions have been answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be handled in a negative way if I do so.
- I may be asked to leave the study before it has finished, if the researcher feels it is in the best interest, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) ..... 20....

.....  
**Signature of participant**

.....  
**Signature of witness**

#### **Declaration by person obtaining consent**

I (*name*) ..... declare that:

- I clearly and in detail explained the information in this document to .....
- I did/did not use an interpreter.
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I gave him/her time to discuss it with others if he/she wished to do so.

Signed at (*place*) ..... on (*date*) ..... 20....

.....  
**Signature of person obtaining consent**

.....  
**Signature of witness**

**Declaration by researcher**

I (*name*) ..... declare that:

- I had the information in this document explained by ..... who I trained for this purpose.
- I did/did not use an interpreter
- I encouraged him/her to ask questions and took adequate time to answer them
- The informed consent was obtained by an independent person.
- I am satisfied that he/she adequately understands all aspects of the research, as described above.
- I am satisfied that he/she had time to discuss it with others if he/she wished to do so.

Signed at (*place*) ..... on (*date*) ..... 20....

.....  
**Signature of researcher**

.....  
**Signature of witness**

## ANNEXURE C: SUBJECT DIARY

### Patient diary

**Subject number:**

**Treatment cycle:**

**Date:**

#### Instructions for completing this diary

**Vomiting:**

Actual expulsion of stomach contents

**Retching / dry heaves**

An attempt to vomit with no contents coming out

**Nausea**

The feeling that you might vomit

A new emetic episode begins after at least 1 minute has passed with no vomiting and no dry heaves. If episodes takes places within one minute of each other, it counts as one episode.

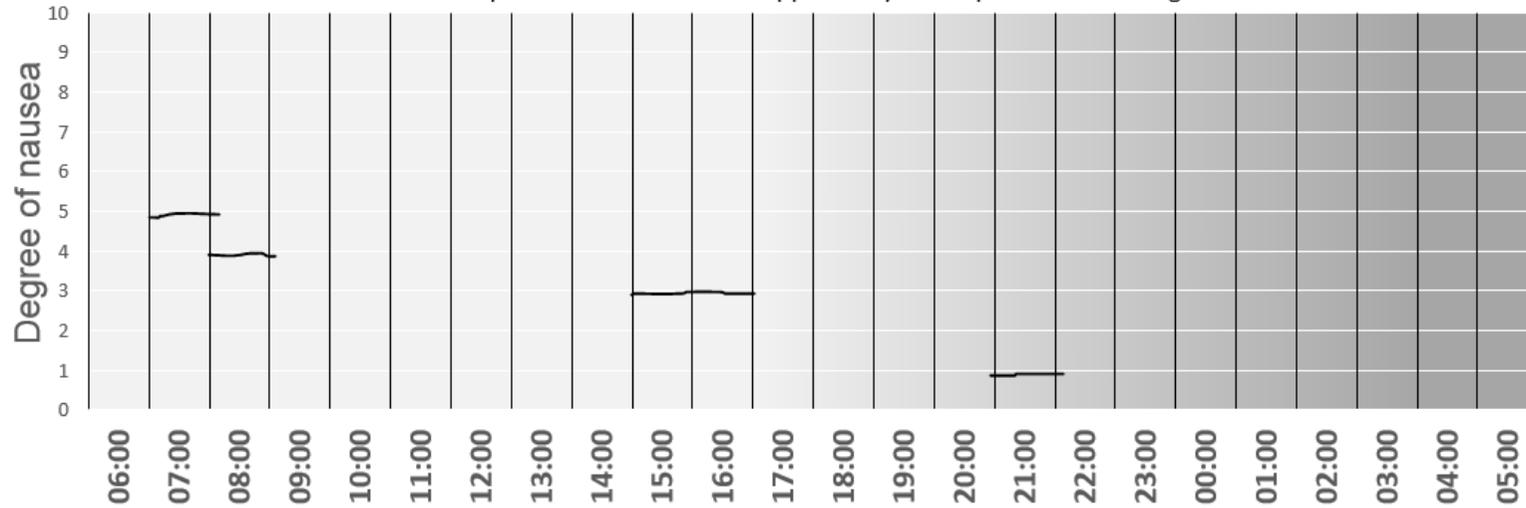
1. Please record the time whenever you have vomit or have dry heaves
2. Please record the time of feeling nausea and the intensity of nausea during the course of every day
3. Please record all additional medication taken for nausea/vomiting

Use the scale in the diary to indicate your nausea level out of ten with;

**'0' = no nausea at all**  
**'10' = nausea at its worst**

To illustrate the scale, look at the example below:

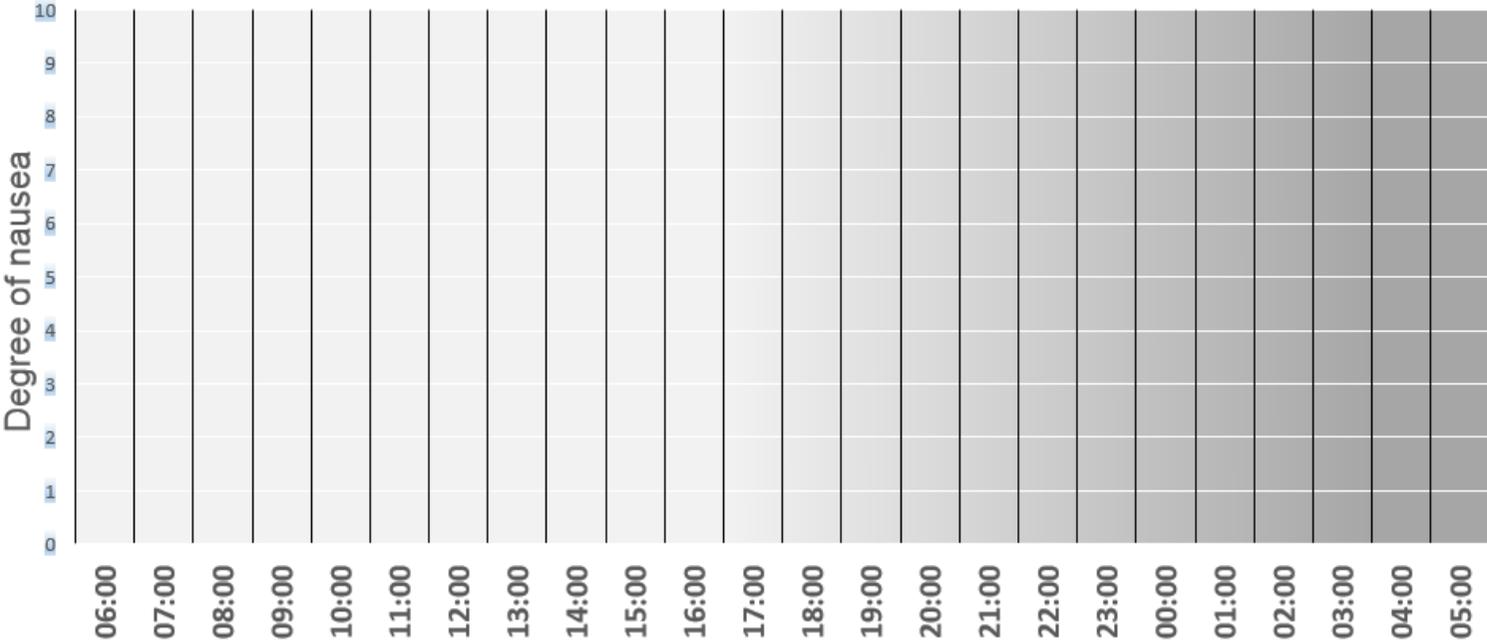
- In the morning between 7am and 8am, patient had nausea at a level of 5/10
  - Patient's nausea improved between 8am and 9am at level of 4/10
- From 2pm-4pm in the afternoon, patient had nausea levels of 2/10, lasting 2 hours
  - The patients nausea level dropped to 1/10 at 9pm in the evening



Subject diary – day 1

How much nausea do you have over 24-hours?

Day 1- chemo infusion: \_\_/\_\_/201\_ Time started: \_\_:\_\_



Please record any episodes of vomiting or dry heaves that you had on day 1

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

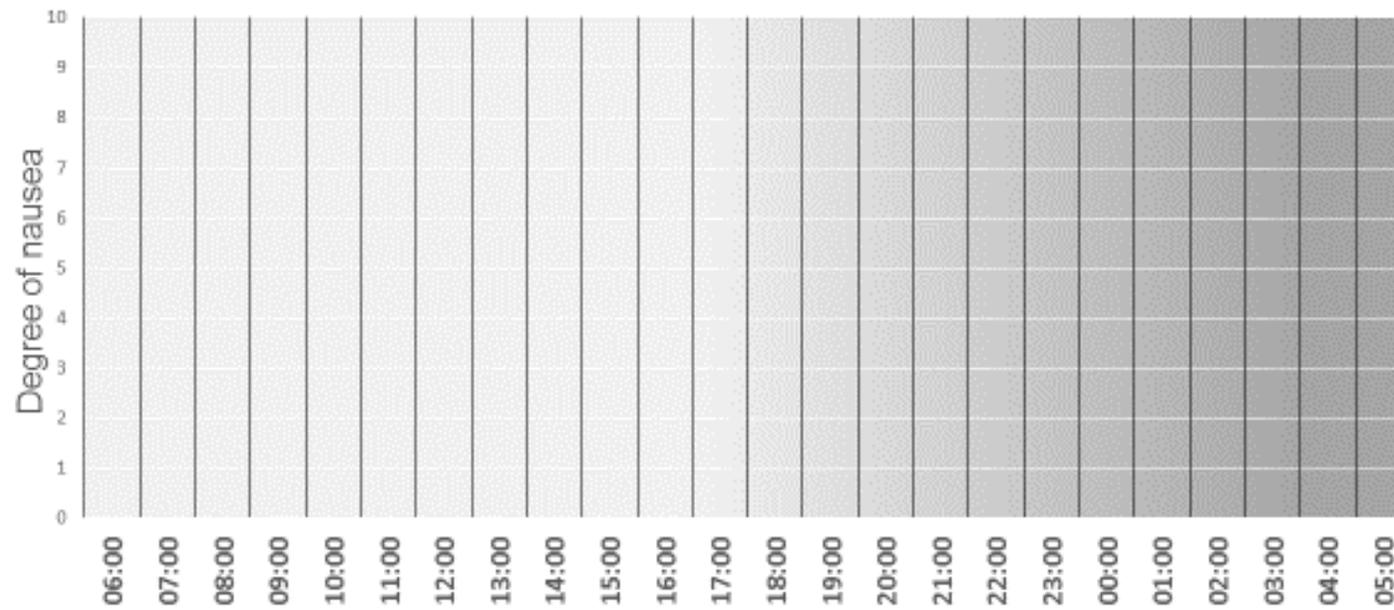
Please record any additional medication taken on day 1 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm

Subject diary – day 2

How much nausea do you have over 24-hours?

Day 2: \_\_/\_\_/201\_\_



Please record any episodes of vomiting or dry heaves that you had on day 2

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

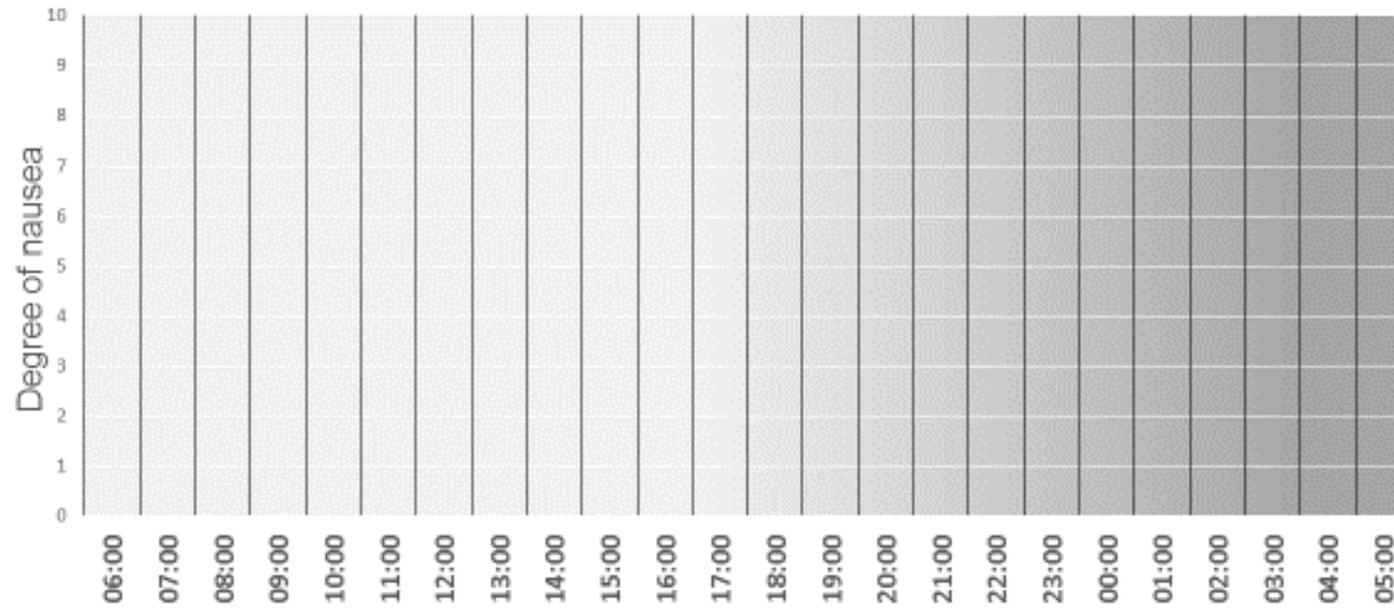
Please record any additional medication taken on day 2 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm

Subject diary – day 3

How much nausea do you have over 24-hours?

Day 3: \_\_/\_\_/201\_\_



Please record any episodes of vomiting or dry heaves that you had on day 3

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

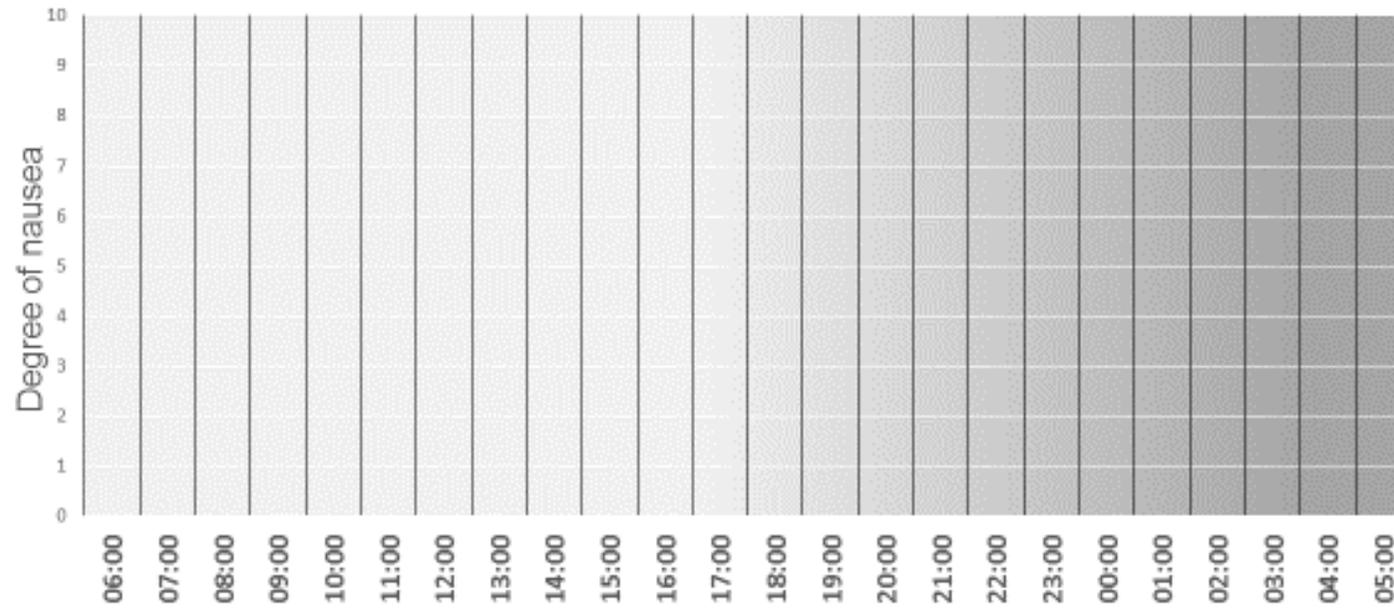
Please record any additional medication taken on day 3 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm

Subject diary – day 4

How much nausea do you have over 24-hours?

Day 4: \_\_/\_\_/201\_\_



Please record any episodes of vomiting or dry heaves that you had on day 4

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

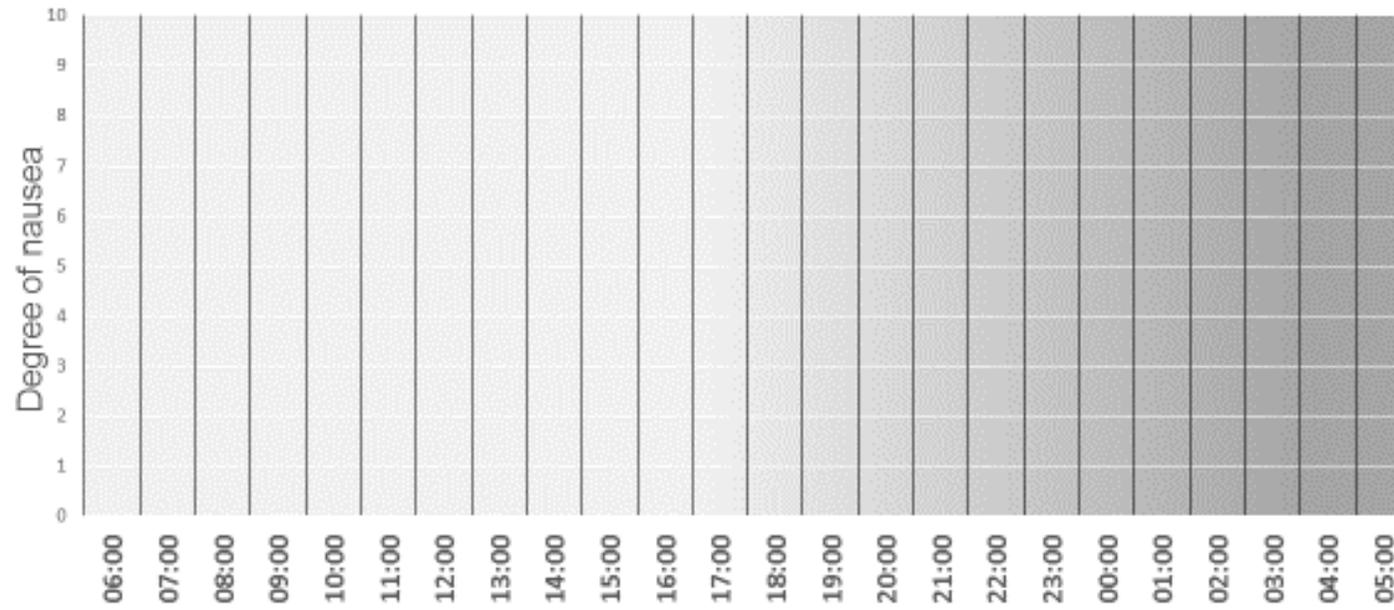
Please record any additional medication taken on day 4 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm

Subject diary – day 5

How much nausea do you have over 24-hours?

Day 5: \_\_/\_\_/201\_\_



Please record any episodes of vomiting or dry heaves that you had on day 5

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

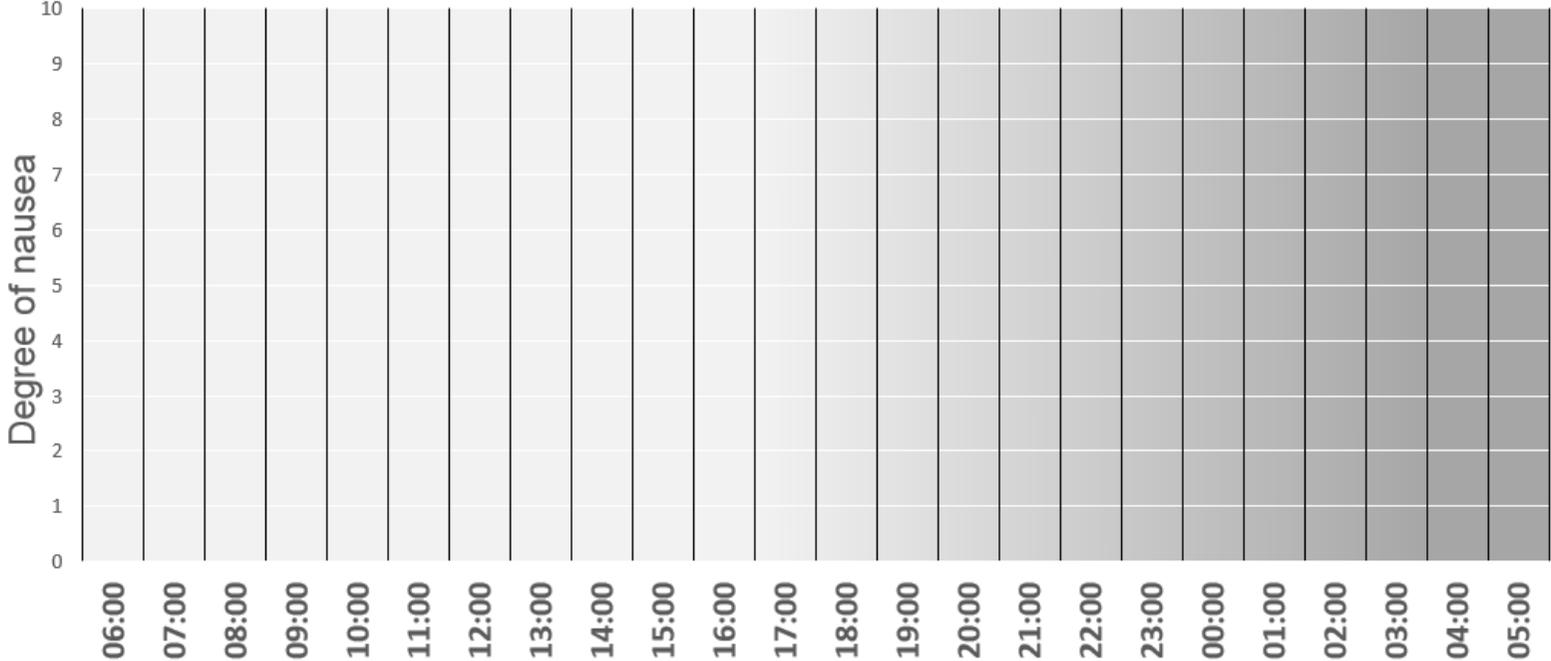
Please record any additional medication taken on day 5 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm

Subject diary – day 7

How much nausea do you have over 24-hours?

Day 7: \_\_/\_\_/201\_\_



Please record any episodes of vomiting or dry heaves that you had on day 5

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

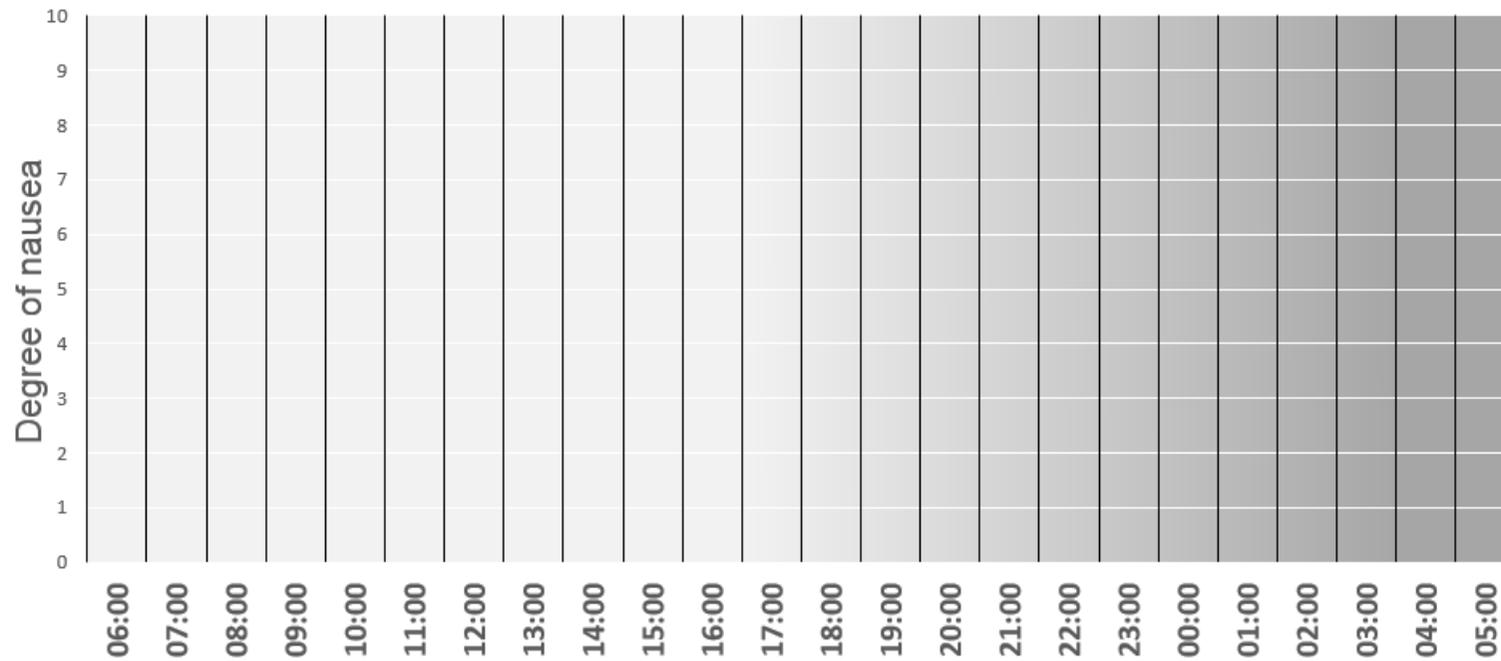
Please record any additional medication taken on day 5 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm

Subject Diary – Day 10

How much nausea do you have over 24-hours?

Day 10: \_\_/\_\_/201\_\_



Please record any episodes of vomiting or dry heaves that you had on day 5

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

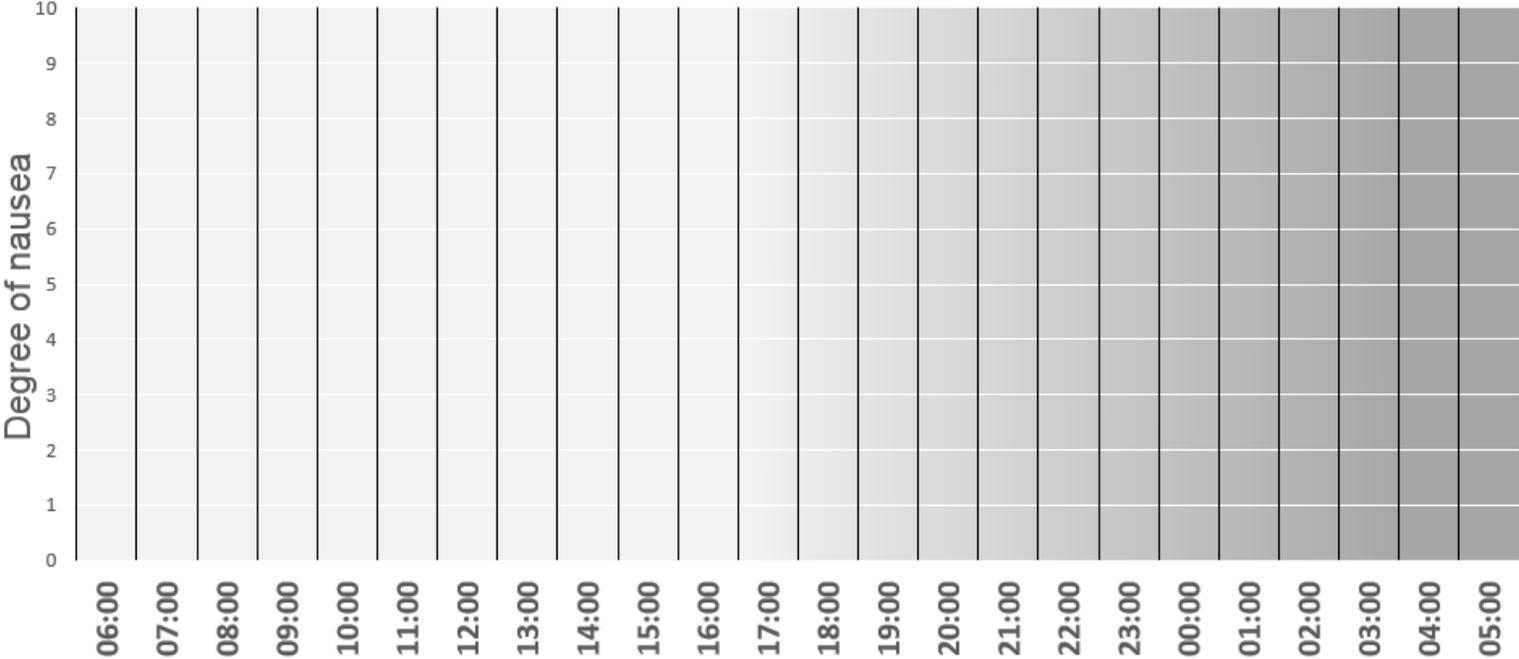
Please record any additional medication taken on day 5 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm

Subject diary – day before chemo (cycle 2/3)

How much nausea do you have over 24-hours?

Day before next infusion: \_\_/\_\_/201\_\_



Please record any episodes of vomiting or dry heaves that you had on day 5

	Time:
1.	__:__ am/pm
2.	__:__ am/pm
3.	__:__ am/pm
4.	__:__ am/pm
5.	__:__ am/pm
6.	__:__ am/pm
7.	__:__ am/pm
8.	__:__ am/pm
9.	__:__ am/pm

Please record any additional medication taken on day 5 for nausea / vomiting

Name of medication	Quantity	Time
		__:__ am/pm



## ANNEXURE E: PATIENT INFORMATION SHEET – DEMOGRAPHIC AND CLINICAL INFORMATION

Subject number:	Date of questionnaire:
Year of birth	19__
Gender	Male / Female
Ethnicity	Caucasian / African / Asian / Other
Cancer type & stage	
ECOG	
Previous chemotherapy/ radiotherapy?	
Treatment & cycles during this survey	
Anti-emetic prophylaxis with this treatment	
Concomitant medication • Proton pump inhibitor • Other	
Co-morbidities	
Risk Factors • Previous CINV • Surgery in the last 14 days • History of motion sickness • History of morning sickness • History of alcohol abuse • Alcohol use in the last 2 years	Yes/no Yes/No None/Moderate/Severe None/Moderate/Severe Yes/No None / <7 per week / 1-4 per day / >4 per day
Other	



# ANNEXURE G: PERMISSION FOR STUDY LOCATION

[Redacted]

Dip. In Med. (B.A.) H.Med. (Int.Med.) (Wits.)

**SPECIALIST PHYSICIAN - MEDICAL ONCOLOGIST**  
Practice Number: 2306182

CONSULTING ROOMS

POSTAL ADDRESS

[Redacted]

26 May 2016

MUSA ethics committee – NWU

**RE: Permission from site to do research**

The Medical Oncology Centre of Rosebank herewith gives permission to Teresa Smit to carry out her research for her MPharm at the clinic.

The clinic is continuously running clinical trials and the site and personnel involved comply with the necessary requirements as per regulation.

Please contact me with any queries in this regard

Kind regards



Dr BL Rapport

## ANNEXURE H: PERMISSION TO USE FIGURE 2

**From:** Teresa Smit <[teresasmit@mweb.co.za](mailto:teresasmit@mweb.co.za)>  
**Sent:** 17 September 2018 10:06 AM  
**To:** 'Barbara Slusher' <[bslusher@jhmi.edu](mailto:bslusher@jhmi.edu)>  
**Cc:** [pharmacist@rapoport.co.za](mailto:pharmacist@rapoport.co.za)  
**Subject:** RE: Permission to use Picture

Much appreciated,

Regards Teresa

**From:** Barbara Slusher <[bslusher@jhmi.edu](mailto:bslusher@jhmi.edu)>  
**Sent:** 17 September 2018 03:47 AM  
**To:** Teresa Smit <[teresasmit@mweb.co.za](mailto:teresasmit@mweb.co.za)>  
**Cc:** [pharmacist@rapoport.co.za](mailto:pharmacist@rapoport.co.za)  
**Subject:** RE: Permission to use Picture

Certainly, that is fine with me.

**From:** Teresa Smit [<mailto:teresasmit@mweb.co.za>]  
**Sent:** Sunday, September 16, 2018 9:38 PM  
**To:** Barbara Slusher <[bslusher@jhmi.edu](mailto:bslusher@jhmi.edu)>  
**Cc:** [pharmacist@rapoport.co.za](mailto:pharmacist@rapoport.co.za)  
**Subject:** Permission to use Picture  
Dear Dr [Slusher](mailto:bslusher@jhmi.edu)

My name is Teresa Smit, I am currently completing my degree *Master of Pharmacy* titled "The prevalence and configuration of nausea in patients receiving intravenous chemotherapy in a private oncology centre in South Africa".

With your permission, can I use Figure 1 from your article "Emerging treatments in chemotherapy-induced nausea and vomiting" in my thesis? I find this picture helpful in describing the pathophysiology and mechanism of nausea and vomiting.

I appreciate your consideration,

Kind Regards

Teresa Smit

Pharmacist

+27 11 880 4222/3



The Medical Oncology Centre  
of Rosebank  
Personalised Cancer Care

## ANNEXURE I: PERMISSION TO USE FIGURE 3



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**SPRINGER NATURE**

**Title:** Drug Treatment of Chemotherapy-Induced Delayed Emesis

**Author:** Ranjana Tavorath, Paul Hesketh

**Publication:** Drugs

**Publisher:** Springer Nature

**Date:** Jan 1, 1996

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## ANNEXURE J: CLASSIFICATION OF EMETOGENIC POTENTIAL OF CHEMOTHERAPY AGENTS

Classification of emetogenic potential of single intravenous chemotherapy agents into high emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), low emetogenic chemotherapy (LEC) and minimal emetogenic chemotherapy (Roila <i>et al.</i> , 2016:121).		
High emetogenic potential (HEC)		
Anthracycline/cyclophosphamide combinations Carmustine	Cisplatin Cyclophosphamide $\geq$ 1500mg/m <sup>2</sup>	Dacarbazine Mechlorethamine Streptozocin
Moderate emetogenic potential (MEC)		
Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide < 1500mg/m <sup>2</sup>	Cytarabine > 1000mg/m <sup>2</sup> Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide	Irinotecan Oxaliplatin Romidepsin Temozolomide Thiotepa Trabectedin
Low emetogenic potential (LEC)		
Aflibercept Belinostat Blinatumomab Bortezomib Brentuximab Cabazitaxel Carfilzomib Catumaxomab Cetuximab Cytarabine $\leq$ 1000mg/m <sup>2</sup>	Docetaxel Eribulin Etoposide 5-Fluorouracil Gemcitabine Ipilimumab Ixabepilone Methotrexate Mitomycin Mitoxantrone	Nab-paclitaxel Paclitaxel Panitumumab Pemetrexed Pegylated liposomal doxorubicin Pertuzumab Temsirrolimus Topotecan Trastuzumab-emtansine Vinglunine
Minimal emetogenic potential		
Bevacizumab Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Cladribine	Fludarabine Nivolumab Ofatumumab Pembrolizumab Pixantrone Pralatrexate	Rituximab Trastuzumab Vinblastine Vincristine Vinorelbine

## ANNEXURE K: CURRENT ANTIEMETIC GUIDELINE RECOMMENDATION

<b>ASCO</b> (Updated October 2017)	<b>ESMO/MASCC</b> (Updated March 2016)	<b>NCCN</b> (updated June 2018)
<b>HEC (Including AC combinations)</b>		
Dexamethasone +  5-HT <sub>3</sub> Receptor Antagonist +  NK-1 Receptor Antagonist +  Olanzapine	Dexamethasone +  5-HT <sub>3</sub> Receptor Antagonist +  NK-1 Receptor Antagonist  <b>For delayed CINV:</b> Dexamethasone + Metoclopramide  <b>For delayed CINV with AC:</b> Dexamethasone + NK-1 Receptor Antagonist (aprepitant)	Dexamethasone +  5-HT <sub>3</sub> Receptor Antagonist  +  NK-1 Receptor Antagonist ±  Olanzapine
<b>MEC</b>		
<b>Carboplatin area under the curve (AUC) ≥ 4mg/ml:</b>  Dexamethasone + 5-HT <sub>3</sub> Receptor Antagonist + NK-1 Receptor Antagonist	<b>Treatment with carboplatin:</b>  Dexamethasone + 5-HT <sub>3</sub> Receptor Antagonist + NK-1 Receptor Antagonist	Dexamethasone + palonosetron + olanzapine  OR  Dexamethasone + 5-HT <sub>3</sub> Receptor Antagonist  +  Olanzapine
<b>Treatment with oxaliplatin, cyclophosphamide or anthracycline:</b>  Add dexamethasone on day 2 + day 3	<b>Patients with delayed CINV:</b>  Add dexamethasone on day 2 + day 3	<b>Patients with additional risk factors:</b>  Dexamethasone + 5-HT <sub>3</sub> Receptor Antagonist  +  NK-1 Receptor Antagonist
<b>All other MEC:</b>  Dexamethasone + 5-HT <sub>3</sub> Receptor Antagonist	<b>All other MEC:</b>  Dexamethasone + 5-HT <sub>3</sub> Receptor Antagonist	<b>All other MEC:</b>  Dexamethasone + 5-HT <sub>3</sub> Receptor Antagonist

<b>LEC</b>		
Dexamethasone or 5-HT <sub>3</sub> Receptor Antagonist	Dexamethasone or 5-HT <sub>3</sub> Receptor Antagonist or Dopamine Receptor Antagonist	Dexamethasone or 5-HT <sub>3</sub> Receptor Antagonist or prochlorperazine or metoclopramide
<b>Minimal</b>		
No prophylactic antiemetic	No prophylactic antiemetic	No prophylactic antiemetic
<b>Breakthrough CINV</b>		
Olanzapine	Olanzapine	Add one agent from a different drug class to the current treatment (olanzapine, benzodiazepine, cannabinoid, haloperidol, metoclopramide, phenothiazine, 5-HT <sub>3</sub> Receptor Antagonist or dexamethasone).
<b>Anticipatory CINV</b>		
Emphasis on best possible control for acute and delayed CINV to prevent anticipatory CINV.  Behavioural therapy with systematic desensitization.	Emphasis on best possible control for acute and delayed CINV to prevent anticipatory CINV.  Behavioural therapies (e.g. muscle relaxation, hypnosis)  Benzodiazepines	Prevention is key, by using optimal antiemetic therapy during every cycle.  Behavioural therapy, acupuncture, acupressure, anxiolytic therapy.

<b>Complimentary / alternative treatments</b>		
Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture, and acupressure for the prevention of CINV in patients with cancer.		
<b>Cannabinoids</b>		
Evidence remains insufficient for a recommendation regarding treatment with medical marijuana for a prevention of CINV in patients who receive chemotherapy.		Cannabinoids (dronabinol and nabilone) are approved by the FDA for refractory CINV when patients have not responded to conventional antiemetic agents.

## ANNEXURE L: PROOF OF TECHNICAL EDITING

---

TO WHOM IT MAY CONCERN

I hereby declare that the dissertation titled:

**The prevalence and configuration of nausea in patients  
receiving intravenous chemotherapy in a private oncology  
centre in South Africa**

by

**T Smit  
10775927**

has been technically edited by myself, which includes all tables and figures as well as the layout of the document's contents.

E Oosthuizen

December 2018

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