The assessment of hydration states in advanced cancer patients using novel technology: the evaluation of bioelectrical impedance vector analysis (BIVA) in the palliative care setting

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By

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ABSTRACT

HYDRATION IN ADVANCED CANCER

The role of hydration in causing or alleviating suffering in patients with advanced cancer is poorly understood and remains controversial. Most dying cancer patients have reduced oral intake in the last days of life. This may be related to symptoms arising from the cancer or its treatment, such as dysphagia, anorexia, nausea, vomiting, or mechanical problems such as bowel obstruction. Accordingly, the subject of clinically assisted hydration (CAH) is emotive amongst patients and their carers, with the omission or withdrawal of CAH potentially viewed as hastening death in some instances. Current hydration assessment methods are limited in cancer patients approaching death. Bioelectrical impedance vector analysis (BIVA) is an accurate validated method of assessing body composition; however its clinical use in advanced cancer is uncertain. This study aims to measure hydration in advanced cancer patients using BIVA, in order, to determine the relationship between symptoms, physical signs and biochemistry.

BIVA was used to evaluate hydration in advanced cancer patients within a hospice in the UK. Total body water (TBW) was estimated using the impedance index (Height$^2$/Resistance [H$^2$/R]). Regression analysis determined the predictive properties of clinical variables on H$^2$/R. Assessed items included: performance status (ECOG), symptoms (Burge-4 score), physical signs (Morita Dehydration Score) and biochemistry.

Ninety patients participated (recruitment rate = 76.3%). Hydration status was normal in 43 (47.8%), ‘more hydrated’ in 37 (41.1%) and ‘less hydrated’ in 10 (11.1%) patients. A multiple regression analysis was conducted. H$^2$/R was significantly predicted by female gender (Beta = -13.85, p<.001), the Burge-4 score (Beta = -0.29, p=.04), the Morita dehydration score (Beta = -2.55, p=.02) and oedema (Beta = 2.55, p<.001). Median survival was significantly shorter in ‘less
hydrated' patients (44 vs. 68 days; \( p=0.04 \)) and in pre-renal failure (44 vs. 100 days; \( p=0.003 \)). Higher values of \( H^2/R \) were associated with improved survival (HR=0.98 [95%CI= .96, .99], \( p=0.01 \)).

The results demonstrate that in advanced cancer, hydration status (as measured by \( H^2/R \) and BIVA) relates to clinically measurable signs and symptoms. Lower TBW volume was associated with female gender and also linked with higher scores for symptoms and physical signs. Higher TBW was associated with oedema. \( H^2/R \), BIVA and pre-renal failure were independent predictors of survival. Further work is needed to determine how BIVA can be used to guide the management of fluid states in advanced cancer.
ACKNOWLEDGEMENTS

Firstly I offer my sincerest gratitude to my supervisor, Professor John Ellershaw who has guided me throughout my thesis with his expertise, patience and supportive feedback whilst allowing room for me to develop my research project and work in my own way. I thank him for his support in coordinating funding for my research fellowship. I attribute the completion of this research project and thesis to his encouragement and effort. One simply could not wish for a better or more supportive supervisor.

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I thank all the patients who selflessly volunteered to participate in the study. I have learnt so much from them and I hope their contribution will go to benefit the lives of others. I thank all the staff in the Marie Curie Hospice Liverpool and my work colleagues at the Marie Curie Palliative Care Institute Liverpool.

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<th>Abbreviation</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>ACB</td>
<td>Anticholinergic Burden Score</td>
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<tr>
<td>APM</td>
<td>Association of Palliative Medicine</td>
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<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
</tr>
<tr>
<td>BIS</td>
<td>Bioelectrical impedance spectroscopy</td>
</tr>
<tr>
<td>BIVA</td>
<td>Bioelectrical impedance vector analysis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BNF</td>
<td>British National Formulary</td>
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<tr>
<td>CAH</td>
<td>Clinically assisted hydration</td>
</tr>
<tr>
<td>Cr</td>
<td>Creatinine</td>
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<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>Db</td>
<td>Bone density</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual energy X-ray absorptiometry</td>
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<tr>
<td>dFFM</td>
<td>Density of fat free mass</td>
</tr>
<tr>
<td>ECOG</td>
<td>European Collaborative Oncology Group Performance Status</td>
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<tr>
<td>ECW</td>
<td>Extracellular water</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESPEN</td>
<td>The European Society for Clinical Nutrition and Metabolism</td>
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<tr>
<td>FM</td>
<td>Fat mass</td>
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<tr>
<td>FFM</td>
<td>Fat free mass</td>
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<tr>
<td>GMC</td>
<td>General Medical Council</td>
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<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>H</td>
<td>Height</td>
</tr>
<tr>
<td>$H^2/R$</td>
<td>Impedance index ($\text{Height}^2/\text{Resistance}$)</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>I</td>
<td>Electrical current</td>
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<tr>
<td>ICW</td>
<td>Intracellular water</td>
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<td>ICP</td>
<td>Integrated Care Pathway</td>
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<td>LACDP</td>
<td>Leadership Alliance for the Care of the Dying Person</td>
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<tr>
<td>LCP</td>
<td>Liverpool Care of the Dying Pathway</td>
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<tr>
<td>LCTU</td>
<td>Liverpool Cancer Trials Unit</td>
</tr>
<tr>
<td>MCHL</td>
<td>Marie Curie Hospice Liverpool</td>
</tr>
<tr>
<td>MCPCIL</td>
<td>Marie Curie Palliative Care Institute Liverpool</td>
</tr>
<tr>
<td>mEq/L</td>
<td>Milliequivalents per liter</td>
</tr>
<tr>
<td>MF-BIA</td>
<td>Multi frequency bioelectrical impedance analysis</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrams</td>
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<tr>
<td>mmol</td>
<td>Millimoles</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>Na</td>
<td>Sodium</td>
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<tr>
<td>NIHR</td>
<td>National Institute for Health and</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>PA</td>
<td>Phase angle</td>
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<tr>
<td>PPC</td>
<td>Preferred priorities of care</td>
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<tr>
<td>R</td>
<td>Resistance</td>
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<tr>
<td>RXc</td>
<td>Resistance/Reactance</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-BIA</td>
<td>Single frequency bioelectrical impedance analysis</td>
</tr>
<tr>
<td>TBW</td>
<td>Total body water</td>
</tr>
<tr>
<td>Δ-TBWdeu</td>
<td>Delta Total body water - deuterium dilution</td>
</tr>
<tr>
<td>Ur</td>
<td>Urea</td>
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<td>Ur:Cr ratio</td>
<td>Urea:creatinine ratio</td>
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<tr>
<td>V</td>
<td>Volume</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>Xc</td>
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AIMS AND OBJECTIVES

AIM

To improve the understanding of hydration states of advanced cancer, through the addition of bioelectrical impedance vector analysis (BIVA) to the best available clinical assessment tools and biochemical investigations.

This aim will be achieved through completion of the following objectives:

OBJECTIVE 1

Bioelectrical impedance analysis (BIA) will be used to evaluate hydration states in individuals with advanced cancer, in order, to determine the relationship of hydration with biochemical investigations, clinical examination and patient self-reported symptoms.

OBJECTIVE 2

To conduct an analysis of BIA data using the method of vector analysis (BIVA) and the RXc graph, in order, to facilitate group comparisons of hydration status according to specific clinical characteristics. Additionally, this analysis will compare hydration states of other cancer populations through use of BIVA data derived from the literature.

OBJECTIVE 3

Survival, from date of first assessment, will be analysed according to BIVA hydration status, the impedance index and clinical biochemistry.

OBJECTIVE 4

An analysis of individuals receiving repeat BIVA assessments will be conducted to evaluate the longitudinal change in hydration status (from first to last assessment) to determine whether this change is associated with survival.
CHAPTER 1: INTRODUCTION

SECTION 1: CARE OF THE DYING IN THE 21st CENTURY

1.1.1 A BRIEF HISTORY OF PALLIATIVE CARE

The World Health Organization (WHO) first formally defined the term palliative care in 1989;\(^1\) this was revised in 2010 to describe palliative care as an approach that: “...improves the quality of life of patients and their families facing the problem anticipated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and social.”\(^2\) This concept of palliative care comes from a history spanning four decades, over which, the subject has gained increasing acceptance within healthcare and society.\(^3\)

Palliative care is a relatively new speciality and originates from the work of key individuals, dating back to the nineteenth century, who endeavoured to improve the care of dying patients, who were often in societies where there was little provision for the infirm and the dying.

In the nineteenth century, Jeanne Garnier, Mary Aikenhead and Rose Hawthorne shared a common purpose in their concern for the care of the dying, and in particular the dying poor. In the countries they resided (France, USA and Australia respectively) they were pivotal in opening homes which cared for the dying. These homes would lead to the establishment of many similar care homes around the world. Although the places they founded did not offer sophisticated medical or nursing care, they created some of the conditions for the development of modern hospices.\(^4\)

The twentieth century saw rapid changes in medicine. Advances in the diagnosis and treatment of disease led to the development of many different medical and
surgical specialities, in which the emphasis was on treatment and rehabilitation. Conditions and disease previously considered as incurable were now potentially curative. Consequently, a shift in the view of medical care emerged, with the inability to cure becoming viewed as a failure. The creation of the United Kingdom (UK) National Health Service (NHS) in 1948 provided a healthcare system which was free at the point of use for all citizens. The effect of the NHS on the UK population was the overall improvement of the health of the nation; this was particularly attributable to better treatment of infectious disease (previously a major cause of mortality) which resulted in a longer life expectancy and the greater risk of the development of age-related illness, such as cancer. At the same time, death in hospital, rather than at home, was becoming the norm and the dying patient was often viewed as a ‘hopeless case’ and failure of medical practice. In the 1960s, Dame Cicely Saunders was instrumental in drawing attention to the end-of-life care needs of patients with advanced cancer. The work of Dame Cicely Saunders, and other pioneers such as John Hinton, Robert Twycross, Elizabeth Kubler Ross and Colin Murray-Parkes, heralded the start of the hospice movement. These hospices aimed to deliver multifaceted care of terminally ill cancer patients and experienced rapid expansion in the 1980s.

Palliative care continued to progress in specialisation. The work of the Macmillan organisation (now Macmillan Cancer Support) and the Marie Curie Memorial Foundation (now Marie Curie Cancer Care) were important in the establishment of a wide range of care and the delivery of education and research. The development of the Association of Palliative Medicine (APM), in addition to the Royal College of Physicians recognising Palliative Medicine as a medical sub-speciality of medicine in 1987, resulted in greater operational capacity and integration of services into the NHS. These factors led to in greater research, education and the elevation of palliative care within general medicine in the United Kingdom. The past decade has seen continual acknowledgement of the need to improve care for patients approaching the end of their lives. In the year 2000, the Department of Health’s NHS Cancer Plan was the first ever comprehensive strategy to tackle the disease in the England. The report outlined the requirements expected of services providing
specialist care to individuals approaching the end of their lives. This was built upon by the NHS End of Life Care Programme (2004 – 2007), the Gold Standards Framework for primary care, the Liverpool Care of the Dying Pathway (LCP), Preferred Priorities of Care (PPC) and the National End of Life Care Strategy in 2008. These reports detail a strategy to facilitate the delivery of high quality palliative care in the UK. Notably, they provide evidence that most people in the UK wish to die at home; however, the reality is that 60% of people currently die in hospital and this is due to increase by approximately 20% due to longer life expectancy and a projected increase in the UK population. Recent analysis suggests a reversal in this trend, with the proportion of home deaths, increasing from 18.4% in 2004 to 20.8% in 2010. This result is partly due to the use of palliative care home services which have been proven to be successful in increasing the likelihood of a home death and reducing symptom burden, without impacting on caregiver grief.

1.1.2 FUTURE CHALLENGES FOR PALLIATIVE CARE DELIVERY

Advances in multimodal cancer-directed treatment have improved survival for metastatic cancer patients. In the Western world the combination of various demographic, health-related and sociological factors will contribute to an increase in morbidity and mortality over the next decade. On a societal level, there is a shift to patient choice. This is combined with increasing awareness and dialogue about the end-of-life care in the media, with an emphasis on supportive care tailored to the individual. Collectively these issues provide several challenges to the future of palliative care provision in Europe.

Different conceptual models of palliative care delivery have been used to define the role of the service. Initially, specialist palliative care (encompassing all hospice and specialist palliative care services) were concentrated on cancer patients who were referred once their disease had reached a point where no further curative treatment was possible. However, as the range of treatments for cancer has grown and palliative care has developed, patients now may continue receiving active treatments as they approach death. A response is to argue that specialist
Palliative care should be available to patients across their disease trajectory (from diagnosis to death) and not just restricted to end of life.\textsuperscript{23, 24} In light of this, the General Medical Council define end-of-life care as a component of palliative care, comprising of the last 12 months of life.\textsuperscript{25}

Historically, palliative care services were focused on those with incurable cancer; however the current view is that palliative care should be available based on need rather than diagnosis. Consequently, palliative care services have expanded to include those with non-malignant disease; this has created several challenges.\textsuperscript{26} Patients with non-malignant disease have needs which may not be met in a system of care that is based on cancer.\textsuperscript{27} The delivery of care for these patients requires a broad range of specialist knowledge, in order to provide appropriate care. Furthermore, non-cancer diseases have varying illness trajectories which may create difficulties in prognostication and advance care planning.\textsuperscript{28, 29} Notable examples include dementia, chronic obstructive pulmonary disease and congestive cardiac failure. Such patients may be prone to acute exacerbations of their condition, which may require active treatment and liaison with other services.\textsuperscript{27}

The combination of an increasing life expectancy and the desire to increase the number of patients receiving end-of-life care at home is challenging. A specific challenge relates to how services will organise care in the future. Palliative care operates from numerous settings, notably hospice, community and hospital; however, the needs of patients, and the availability of services, may differ significantly between these areas. Additionally, certain populations are currently under-represented, such as those from lower socioeconomic classes, ethnic minorities and the homeless.\textsuperscript{30} There is a need to ensure equity of services and access for users wherever they receive care.\textsuperscript{31} Additionally, it is necessary to ensure the ongoing delivery of high quality undergraduate and postgraduate training programmes that are necessary to educate a future workforce that is likely to be generalist.\textsuperscript{32, 33} Care delivery and education needs to be supported with research, in order to generate the evidence base that is required to meet the needs of an increasingly complex population.\textsuperscript{34} Despite the importance of these issues, palliative care receives significantly less research funding compared to other
specialities.\textsuperscript{35} These issues, combined with ongoing financial austerity will create several challenges for the provision of end-of-life care into the future.

\subsection*{1.1.3 Recent Media Coverage of Palliative Care in the United Kingdom}

An Integrated Care Pathway (ICP) determines a structured, locally agreed, multidisciplinary care plan which details essential steps in the care of patients with specific problems.\textsuperscript{36,37} Over the past two decades, the use of ICPs has been adopted in various settings, including those approaching the end of their lives.\textsuperscript{38} Examples of ICPs for the care of the dying include the Liverpool Care Pathway of the Dying Patient (LCP)\textsuperscript{14} and the All Wales Integrated Care Priorities for the Last Days of Life (ICP).\textsuperscript{39} In the UK, the use of ICPs came under scrutiny with sustained concerns about the safety of implementing end-of-life care pathways.\textsuperscript{40} The media highlighted poor examples of care which were attributed to the use of ICPs.\textsuperscript{21,41-44} However, many of the complaints detailed in these accounts were related to poor care and communication issues, which, although are not specific to the ICPs were invariably linked to these tools at the end-of-life.\textsuperscript{45}

The media reported alleged instances of sub-optimal care in which some patients, who were able to drink, were not provided with oral fluids.\textsuperscript{41} Additionally, the rationale of decisions relating to clinically assisted hydration (CAH) for dying patients was debated, with accusations that the non-use (or withdrawal) of CAH was causing some patients to die prematurely of dehydration.\textsuperscript{46} In light of these concerns of poor care, an independent review of the LCP was commissioned by the UK government which set out to evaluate the use of the LCP in the management of dying patients. The review concluded that the LCP should be withdrawn and replaced by individualised care plans for dying patients.\textsuperscript{24} An outcome of the review was the acknowledgement of a lack of research in key areas and the recommendation for greater investment research is needed to improve care of the dying. The review led to the formation of the Leadership alliance for the care of Dying People (LACDP), a coalition of 21 national organisations concerned to ensure high quality, consistent care for people in the last few days and hours of life.\textsuperscript{47} In
June 2014, the LACDP published a Government guidance document entitled ‘One chance to get it right’. This report outlines the future requirements of care for all dying people in England, irrespective of whether organisations were previously using the LCP or not. The approach focuses on putting the dying patient as the focus of the care, through the achievement of five Priorities for Care. The priorities for a person thought to be in the last hours to days of life are as follows:\textsuperscript{47}

1. The possibility that the person is dying is recognised and communicated clearly, decisions made and actions taken in accordance with the person’s needs and wishes, and these are regularly reviewed and decisions revised accordingly.

2. Sensitive communication takes place between staff and the dying person, and those identified as important to them.

3. The dying person, and those identified as important to them, are involved in decisions about treatment and care to the extent that the dying person wants.

4. The needs of families and others identified as important to the dying person are actively explored, respected and met as far as possible.

5. An individual plan of care, which includes food and drink, symptom control and psychological, social and spiritual support, is agreed, co-ordinated and delivered with compassion.

Currently (due to a variety of practical, ethical and methodological issues) there is a lack of research evidence to address these areas.

\subsection{1.1.4 RESEARCH CHALLENGES IN PALLIATIVE CARE}

Palliative care is a relatively young speciality which has developed outside traditional University and NHS systems. Consequently, hospices often lack a research governance infrastructure which limits the potential for research to be conducted in these areas. Formal arrangements for NHS indemnity from neighbouring hospitals is varied by location and is often complex. Palliative care staff may face difficulties in conducting research studies, due to a lack of research training and dedicated research time. The 2011 consultant census by the Royal
College of Physicians revealed that the mean number of academic programmed activities by palliative medicine consultants was almost half that of other specialities (0.4 vs. 0.7). Additionally, there are relatively few clinical academic posts compared to other specialities, with only 15 joint University-NHS academic posts in England. These infrastructural and workforce issues contribute to an environment that is not conducive for research.

Research involving patients who are approaching death is methodologically and ethically challenging. This group of patients often have significant symptomatic burden, including pain, fatigue and psychological distress. Researchers may struggle to engage and recruit participants due to concerns about the ability of patients to comply with assessments and provide consent. Consequently, low levels of recruitment, small sample sizes and high attrition rates often have a deleterious impact on the methodological quality of research. However, there is developing evidence which demonstrates that patients are keen to be involved in palliative care research.

A careful, evidence-based approach is necessary to address the inevitable challenges, which will be posed by an increasingly aged population that will require supportive care towards the end of their lives. Further investment in palliative care research is required to generate the evidence which will improve the care delivered to patients approaching death. Currently, funding for end-of-life and palliative care research is inadequate. Data on UK research funding by National Cancer Research Institute partners in 2010 show that just 0.24% was allocated to palliative and end-of-life care research. Similarly, in 2010 the USA National Cancer Institute only awarded 1% its funding to palliative care research. The disparity in research funding reflects the preferential investment to oncological studies which offer curative and life-sustaining treatment. Whilst this is commendable the outcomes of such studies often focus on survival measures with a lack of importance given to quality-of-life. Consequently, patients may endure treatments which cause significant morbidity, with adverse effects to their quality-of-life, despite an increased chance of survival. Provided with enough information,
patients may opt for measures which aim to improve or maintain their quality-of-life, rather than undergo further aggressive treatments. However, irrespective of the quantity or intensity of treatment, many oncological patients will require palliative care as their condition deteriorates.

The lack of investment in palliative care research may also be a reflection of the lack of attention society has given to dying. In Western society, a combination of demographic and sociological factors has contributed to a lack of focus on end-of-life issues. In the UK, the current population can expect longer life expectancy with fewer children later in life. Additionally, society is reportedly more disparate and less community-engaged compared to previous generations. Consequently, bereavement may not be experienced till later in life which can be a source of fear and trepidation. Individuals affected by disease are more likely than ever to be living by themselves with a lack of support from their local community. Campaigns, such as Dying Matters Coalition coordinated by the National Council for Palliative Care, have attempted to elevate the issue of dying to the public consciousness. The recent media attention to end-of-life issues demonstrates that people are recognising that end-of-life issues are important. However, until society demands that quality-of-life is regarded to be equal in value as survival, it is unlikely to receive appropriate attention or funding. Therefore, the challenge is to engage with society to have an honest debate to encourage investment in end-of-life care and research.

1.1.5 THE NEED FOR HIGH QUALITY RESEARCH IN END-OF-LIFE CARE

There is a need to improve the opportunities for patients to participate in research. Polls conducted by Ipos Mori (a leading market research company in the UK and Ireland) demonstrate that the public are keen to take part in research. However, in the health service there are several barriers which result in patient not being provided with the opportunity. The National Institute for Health Research (NIHR) conducted ‘mystery shopper’ report to evaluate research activity in several healthcare settings. The report highlighted that in the 82 hospitals studied, 91% lacked information about research opportunities for patients. The lack of
opportunities for research may be more prevalent in end-of-life care due to various barriers faced by those in the palliative phase of their illness.\textsuperscript{51} Investment is required to improve research opportunities for patients receiving palliative care in different healthcare and community settings.\textsuperscript{49,61}

Several areas within palliative medicine lack research evidence, which creates complexity and uncertainty for healthcare professionals when attempting to provide best practice to patients. An area lacking evidence involves the clinical assessment and management of hydration in advanced cancer patients.

The independent review of the Liverpool Care of the Dying Pathway (LCP) in the UK notes that many complaints about end-of-life care involved decisions concerning hydration and nutrition.\textsuperscript{24} Decisions surrounding the administration of CAH to patients at the end-of-life can be challenging, with many healthcare professionals, patients and carers presenting differing opinions on appropriate management.\textsuperscript{63-68}

The General Medical Council (GMC) of the UK has released guidance concerning the administration of CAH at the end-of-life for patients who are expected to die within hours or days, and those who are not expected to die within this timeframe. Clinicians are required to assess hydration status in both circumstances.\textsuperscript{25} However, decisions about appropriate management are often difficult due to a limited understanding of hydration mechanisms in advanced cancer, and a lack of evidence to guide healthcare professionals.\textsuperscript{63,68,69}

The lack of evidence in the area of hydration at the end-of-life creates particular challenges. Firstly, without appropriate understanding of how hydration affects quality-of-life it is not possible determine if patients are receiving appropriate care. Furthermore, the limited understanding concerning the management of fluid states creates uncertainty of when CAH should be used or discontinued. In light of these issues, the independent review of the LCP called for research to improve the evidence relating to hydration in palliative care.\textsuperscript{24} The review specifically highlighted the need for studies to evaluate the usefulness of laboratory and other biological evidence, to improve accuracy of diagnostic tools and to conduct mixed
methods trials involving specific hydration interventions. These recommendations were accepted fully by the LACDP.47

Ultimately, the goal of research is the acquisition of new knowledge which will result in tangible benefit for patients. The current societal discussion about palliative care demonstrates many are interested in issues at the end-of-life and desire to see excellent care provided to those requiring support. It is important to acknowledge that an important aspect of care of the dying is the management of hydration. Consequently, for issues concerning hydration at the end of life, it is essential to improve the evidence to improve the care for patients and their families.
SECTION 2: HUMAN BODY COMPOSITION

1.2.1 INTRODUCTION

This section of the thesis outlines the importance of human body composition. It details human body fluid compartments and provides an overview of different methods of its assessment.

1.2.2 BODY FLUID COMPARTMENTS

Water is essential for human life, functioning as a substrate for biochemical reactions and a mechanism of transportation of substances.\(^7^0\) The maintenance of a relatively constant volume and stable composition of body fluids is essential for homeostasis.\(^7^1\) Total Body Water (TBW) is included with the Fat Free Mass (FFM) compartment of the human body. TBW consists of two components including, intracellular water (ICW) and extracellular water (ECW).\(^7^1\)

In the average adult weighing 70kg, water constitutes approximately 60% (42 litres) of body weight.\(^7^0\) Intracellular fluid consists of fluid within body cells and accounts for 40% (28 litres) of total body weight (Figure 1).\(^7^1\) The percentage of body water in an individual is affected by their age, sex, degree of obesity and illness.\(^7^2\) Ageing is associated with a loss of muscle and an increased percentage of body fat, which reduces the percentage of body water.\(^7^2\) Women normally have more body fat than men and therefore contain slightly less body water than men in proportion to their weight.\(^7^0\)\(^7^1\)

The ECW consists of fluid outside of the cells and is classified into three subdivisions: the interstitial compartment, the plasma compartment and the third space. The interstitial compartment is the fluid space that surrounds the cells of a given tissue. It is filled with interstitial fluid which comprises of approximately 15% body weight (10.5 litres). Interstitial fluid is rich in ions, proteins, and nutrients and allows for their movement across the cell membrane. The fluid is continuously exchanged and eventually recollected by the lymphatic channels.\(^7^3\) Blood plasma is the intravascular (blood vessels) part of the ECW; it holds the blood cells in whole blood in suspension and comprises 55% of total blood volume. The third-space
refers to the non-functional space between cells. Fluid will move to this area from the intravascular space (blood vessels) for a variety of reasons, such as an increase in fluid volume, hypoalbuminemia or hyponatraemia. An excess of fluid in the third space may manifest clinically as oedema.

**FIGURE 1: DISTRIBUTION OF BODY WATER FOR AN AVERAGE MALE ADULT WEIGHING 70KG (REPRODUCED WITH PERMISSION)**

![Diagram of body water distribution](image)
1.2.3 BODY COMPOSITION AND ITS IMPORTANCE

Differences in the shape and size of individuals can mark health differences among individuals or population groups. Changes in the structure of normal cellular structure caused by disease can adversely affect function, leading to increased morbidity and eventual mortality. Accurate and reliable measures of anatomical and physiological parameters are important to understand how pathological processes effect health.

The human body can be structured into different levels which provide a structural framework for studying human body composition. There are different models for categorising human body composition, which involve the classification of the human body into either a two or multi-compartment system (Figure 2). A two compartment (2C) model comprises of fat mass (FM) which constitutes the fat content of the body, and fat free mass (FFM) which includes everything that is not body fat.
The 2C model is the most widely used approach to estimate body composition in adults and benefits from its simplicity. The 2C model assumes that the proportions of FFM, water, protein and minerals are stable. Body water is presumed to be 0.732 l/kg (i.e. 73% of soft tissue) and body potassium is estimated at 68.1 meq/kg. These requirements of the 2C model mean that body composition estimates may be inaccurate in situations where the assumptions of the model are not met. This may occur with particular conditions such as aging, pregnancy, weight reduction in obese people, and in various disease states.

The four compartment (4C) model (at an atomic, molecular and cellular level) is the most accurate available measure of body composition and is frequently used as a reference method against which new body composition methods are compared. The 4C model involves the measurement of various factors, including body mass or weight, total body volume, TBW, and bone minerals; however, the 4C method is limited practically as these methods depend on use of specialised laboratory equipment which are not available in routine clinical practice.

Body composition analysis provides various methods to evaluate human nutrition and physiology in relation to the structural multi-compartment model (Figure 2).

1.2.4 BODY COMPOSITION METHODS

Body composition methods comprise of two categories: direct and indirect assessment. Direct methods include total body water measurement, total body potassium counting, neutron activation, body density (Db), dual energy X-ray absorptiometry (DEXA) and imaging methods.

Isotope dilution is a method of measuring total body water and involves the administration of an isotope tracer, either orally or intravenously. The concentration of the tracer excreted in the urine is then measured in order to estimate the total fluid volume.

Total body potassium counting involves measurement of naturally radioactive potassium in the body. Because potassium is found almost entirely within cell
bodies, this measurement can provide an estimate of body cell mass. Consequently, fat-free mass can be estimated once total body potassium is known; however, this assumes a constant concentration of potassium in FFM. Neutron activation involves the use of radiation to cause radioactivity in an atomic cell nucleus. This causes the nucleus to become excited and release gamma rays, which can be used to measure many elements, including carbon, nitrogen, sodium, and calcium.

Body density ($D_b$) is often referred to as a gold standard for body composition measurements. Body density measurements include hydrodensity (also known as underwater weighing) a technique that estimates body composition using measures of body weight, body volume, and residual lung volume. In recent years, the hydrodensity has begun to be replaced by air-displacement plethysmography, where the subject placed in a closed air-filled chamber rather than in water.

DEXA involves the use of two low energy X-ray beams, which provides information about body composition based on the differing radioactive absorptive properties of tissues. This provides a method of quantifying fat, lean, and bone tissue.

Other imaging techniques involve assessment of body compartments with computer tomography (CT) and magnetic resonance imagining (MRI). Indirect assessment methods describe anthropometry and bioelectrical impedance analysis (BIA). Anthropometry provides assessments of body mass, size, shape, and adiposity through measurement of abdominal circumference, body mass index, and skinfold thickness. Although these assessments are simple to perform in clinical environments the accuracy is altered by changes in weight. Furthermore, the findings describe adiposity, and do not measure hydration or muscle mass.

These methods of body composition have several practical limitations (expensive, time consuming, require specialist equipment and staff) which mainly restrict their use to research centres. In light of these issues, BIA has emerged as a popular tool to assess body composition due to characteristics which are comparably favourable to other assessment tools. BIA will be discussed in greater depth within the next section of the thesis.
SECTION 3: BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

1.3.1 INTRODUCTION

The electrical properties of tissues were first described in 1871.\textsuperscript{88} Thomasset demonstrated the relationship of human bio-impedance with TBW.\textsuperscript{89} Tomasset’s studies measured impedance through the use of two subcutaneous needles to generate an impedance index (see below) of TBW.\textsuperscript{89,90} Impedance measurement, using a four pole technique was later developed by Hoffer\textsuperscript{91} and Nyboer.\textsuperscript{92} In 1969, Hoffer et al demonstrated high correlation (r=0.92) between whole body electrical impedance and total body water.\textsuperscript{91} The foundations of BIA were in place by the 1970s, leading to the publication of key work by Lukaski in 1985,\textsuperscript{87} in which BIA was validated against reference methods of deuterium dilution and body potassium measurement. Further research followed, leading to the development of low cost commercial impedance analysers in the 1990s.\textsuperscript{93} Researchers and practitioners were excited about the potential for a low cost, non-invasive, portable method of body composition assessment. The BIA method has a 2 to 4% measurement error,\textsuperscript{94} which is similar to routine laboratory tests.\textsuperscript{95} In 1996, the National Institute of Health in the USA detailed the need for further standardisation of analysers and reference data on the application of BIA technology in practice.\textsuperscript{96} This was further updated in 1999 with an emphasis on improving the science to determine the influence of potential confounding factors with BIA assessments.\textsuperscript{97}

This chapter covers the scientific background and clinical applicability of BIA and BIVA.

1.3.2 THEORECTICAL PRINCIPLES OF BIOELECTRICAL IMPEDANCE ANALYSIS

Living tissue forms a mixture of ionic conductors and inhomogeneous dielectrics (diverse electrical insulator that can be polarised by an applied electric field); consequently, it functions as a material which has a capacitor-like ability to store energy.\textsuperscript{98} Bioelectrical impedance analysis (BIA) uses this attribute to assess body
composition by affecting the physiological flow of ions in response to the application of electrical current.\textsuperscript{99}

The concept of impedance is fundamental to adequately understand non-invasive bioelectrical assessments. Ohm’s Law states that the flow of an electrical current ($I$ - amperes) passing through two points of a conductor is equal to the voltage drop ($V$ - volts) divided by the electrical resistance ($R$ – ohms) between these two points.$\textsuperscript{100}$

$I = V/R$ or $R = V/I$

This concept is based on the introduction of a direct current into a simple conductor with a cylindrical shape. If the current remains constant, the change in voltage across the circuit is equal to the change in the resistance to the current flow. The application of Ohm’s law to an alternating current creates the concept of electrical impedance ($Z$), or just simply the term ‘impedance’:

$Z = V/I$

In humans, impedance of a physiological electrical circuit consists of two parameters: Resistance ($R$ - the opposition of an alternating current through intra- and extracellular ionic solutions, representing the real part of $Z$) and Reactance ($Xc$ – the capacitive component of tissue interfaces, and cell membranes and organelles, representing the imaginary part of $Z$).\textsuperscript{101} Generally, higher $R$ indicates more fat mass (and lower body water); whereas healthy lean tissue is characterised by lower resistance. Lower $Xc$ indicates a breakdown in a cell membranes’ permeability whereas higher $Xc$ indicates healthier tissue. The arc tangent ($Xc/R$), also known as Phase Angle (PA), is a derived measure obtained from the relationship between the direct measures of $R$ and $Xc$ (Figure 3).\textsuperscript{102} The PA is the geometrical representation of the phase shift attributable to the measured electrical current that is stored by the cell membranes, causing the current to lag behind the voltage.\textsuperscript{103,104}
Several electrical circuits have been used to describe the behaviour of biological tissues. Examples include the arrangement of R and capacitance in series or parallel circuits, whilst other models are more complex. The electrical circuit commonly used to describe the bio-impedance model was proposed by Fricke and expanded by Cole. This model describes an electrical circuit that is representative of anatomical and physical processes which is derived from theoretical mathematical equations. In the bio-impedance model, the circuit describes extracellular and intracellular ionic fluids as parallel resistors (a component that determines the flow of electricity in a circuit element) with the cell membrane functioning as the capacitor (an electrical component used to store electrical charge) (Figure 4).

R and Xc can be measured over a range of frequencies (most single-frequency BIA analysers operate at 50-kHz). The volume of intra and extracellular ionic solutions is (inversely) related to the R component of Z. The amount of soft tissue structures containing the solutions is (directly) related to the Xc component of Z. At low frequencies (<50 kHz), the electrical current cannot penetrate cell membranes and, therefore, can be used to predict extracellular water (responsible for R of the body’s R). At infinite frequency (or very high frequency), the cell membrane acts as a (near) perfect capacitor; this allows current to penetrate cell membrane to
estimate both intracellular and extracellular fluid compartments (representing $R_{\text{inf}}$ of total $R$). \cite{10,11,111}

**FIGURE 4: DIAGRAM TO ILLUSTRATE THE EQUIVALENT ELECTRICAL CIRCUIT TO DESCRIBE THE BIOELECTRICAL COMPONENTS OF A CELL**

When a radiofrequency, alternating current, is applied to the body, it is attenuated by water and electrolytes in the extracellular ($R_e$) and intracellular ($R_i$) fluids and characterised as resistance ($R$). The current is stored and released at cell membranes; it is measured as reactance or cellular capacitance ($C_m$). Both resistance and reactance are frequency dependent. Reproduced with permission. \cite{19}

**1.3.3 USE OF BIA TO PREDICT FLUID VOLUMES**

BIA is able to predict fluid volumes using the principle that the impedance ($Z$) of a cylindrical conductor corresponds to its length ($L$), cross-sectional area and the applied signal frequency. \cite{112} The volume (impedance index) is obtained by means of the Nyboer formula: \cite{92} $\text{Volume} = \text{height} \times (\text{height})^2 / R$. Further information about the calculation of the impedance index is presented in Appendix 1.

**1.3.4 THEORECTICAL IMPEDANCE MODELS**

In order to improve accuracy of the impedance assessment, various models have been developed on account of theoretical properties of tissues which may affect impedance. Consequently, bio-impedance assessments may consist of either a simple assessment at a fixed frequency (i.e. single frequency BIA at 50kHz) or
alternative methods. These alternative methods include the Cole-Cole and the Hanai methods.

The theoretical basis of impedance utilises the concept of $R_0$ and $R_{inf}$ levels of $R$. However, several practical aspects prevent the use of these frequencies of $R$ for impedance assessments. The Cole-Cole method predicts the ideal measurement frequencies (i.e. the Cole–Cole plot). In this model $R_0$ represents the $R$ of the extracellular fluid and $R_{inf}$ represents the combined $R$ of ICW and ECW (i.e. TBW). At 50 kHz, the current passes through both ICW and ECW, although the proportion varies depending on the characteristics of tissues.

Another parallel model, proposed by Hanai, acknowledges the effect of ‘mixing’ on electrical conduction. Mixing theory predicts that the $R$ of fluids conducting electricity increases as the amount of non-conducting material increases. This means that electrical current will encounter more resistance as it travels around non-conducting material, such as cells in the human body. Further assumptions (i.e. body density and ratio of intracellular and extracellular resistivities are presumed to be constant) are required to extrapolate the in-vitro Hanai formula for use in vivo models. Although the intended purpose of modelling is to improve accuracy of impedance assessments the improvement seen Cole-Cole and Hanai methods may have little advantage over impedance values measured at fixed frequencies due to estimation errors in the modelled data.

### 1.3.5 VALIDATION OF BIA

Extensive validation studies have taken place to evaluate the relationship of BIA to both direct and indirect reference body composition methods. In 1969 Hoffer et al demonstrated high correlation ($r=0.92$) between whole body electrical impedance and TBW. The foundations of BIA were in place by the 1970s, leading to the publication of many validation studies over the following decade. $H^2/R$ has been found to be a strong predictor of TBW when evaluated against direct reference methods assessment. This index was found to explain 99% of variation of TBW in a cross sectional analysis of a mixed heterozygous population (consisting of adults, pre-pubertal children, pre-school children and premature low birth-
weight neonates) and reported to be the best single predictor of TBW or density of FFM (dFFM) by multiple regression in validation studies involving specific population groups. Specifically in cancer patients, BIA-derived changes in $H^2/R$ significantly predict changes in TBW assessed by deuterium dilution.

1.3.6 USE OF BIA PREDICTION EQUATIONS

BIA, as an indirect method of assessment, simplifies the human body as one cylinder. However, the body is more accurately described as five anatomical cylinders (two arms, two legs and trunk). Differences in body composition occur between groups, based on various factors (unaccounted for by the BIA 2C model), such as gender, ethnicity, age and body mass index. The estimation of the human body compartments from BIA requires adjustment using regression analysis, which aims to improve prediction accuracy by taking account of factors known to affect the BIA 2C model. Consequently, greater accuracy of body composition estimates are obtained through the addition of variables (e.g. weight, height, age, sex and ethnicity) to equations to adjust for potential differences between individuals and the relative underrepresentation of the trunk by whole body impedance.

Therefore, although $H^2/R$ is proportional to TBW it requires refinement (via regression equations) to accurately predict volume. These prediction equations have been developed using linear regression and adhere to basic assumptions including: the shape of the body, the relationship between trunk and leg lengths, the level of hydration (as soft tissue hydration is estimated at 73%\(^{80}\)) and fat fraction. No universal equation exists for different populations; therefore, specific validated equations need to be selected in reference to the individual's age, ethnicity and the clinical condition being studied. Kyle et al\(^{119}\) has summarized the prediction equations that are available for use in a variety of populations. All equations have been validated against reference methods with good accuracy. However, prediction equations are not suitable in situations where the basic assumptions of the bio-impedance method are not met. Many cancer patients are at extremes of body mass and hydration; therefore, prediction equations are not suitable in these patients.
1.3.7 DIFFERENT METHODS OF BIA

Different methods of BIA are available. The single frequency (SF) is the most simple, comprising of an alternating current of 50kHz applied to the participant through four electrodes (typically comprising of two hand and two foot electrodes) on the skin. The method estimates TBW through the measuring the sum resistance to ECW and ICW. SF-BIA is popular because if its simplicity and standardised approach.

At 50 kHz BIA does not measure TBW but provides a weighted sum of ECW and ICW resistivities. The application of prediction equations and mixture theory to the SF-BIA method facilitates estimation of FFM and TBW; however, it is unable to provide detail of ICW volume. Furthermore, as the 50-kHz current does penetrate tissue completely it is unable to measure entire muscle volume.

Multi-frequency BIA (MF-BIA) uses several impedance frequencies i.e. (0, 1, 5, 50, 100, 200 to 500 kHz) to estimate FFM, TBW, ICW and ECW. MF-BIA is based on the principle that the body’s R is dependent on the frequency of the alternating current applied. Low frequencies (<50kHz) enable quantification of ECW whereas higher frequencies (>200kHz) enables evaluation of ICW volume. Empirical linear regression models are used to estimate subject results.

Bioelectrical impedance spectroscopy (BIS) uses a series of frequencies according to the principle of the Cole-Cole model and Hanai formula to generate relationships between R and body fluid compartments. Up to 256 impedance frequencies are used to calculate $R_0$ and $R_{inf}$ frequencies, allowing for the prediction of ICW, ECF and TBW volumes.

Another application of BIA is termed ‘segmental BIA’, which involves use of additional BIA electrodes on the limbs in order to evaluate body composition specific to a particular segment of the body. This method is to overcome the potential variation in assessment attributable to differences in trunk of the body as it only contributes 10% to whole body impedance despite representing up to 50% of body mass. The method may be useful in the evaluation of conditions.
associated with anatomically defined fluid shifts, such as post-surgery, renal failure and ascites.93

The main theoretical advantage that MF-BIA and BIS offers compared to SF-BIA is that they provide direct quantification of the ICW compartment (rather than through estimation of TBW and ECW volumes of SF-BIA) which enables more in-depth evaluation fluid shifts within different fluid compartments.93 111 However, there is disagreement about the reproducibility of these different methods of these compared to SF-BIA. There are some discrepancies that emerge from the prediction of different fluid compartments according to different clinical scenarios.116 119 This is notable with BIS, where outcomes of TBW can vary significantly depending on which BIS method is used.141 A potential drawback of all of these models is the dependence on formulae and regression equations (typically based on healthy individuals) which rely on assumptions about their physiological status. These are limited in advanced cancer patients as some of the fundamental assumptions may be voided (for example, the individual may be at extremes of weight and hydration status).
SECTION 4: BIOELECTRICAL IMPEDANCE VECTOR ANALYSIS (BIVA)

1.4.1 INTRODUCTION

Further useful information about BIA is possible through analysis of raw bioimpedance measurements. Piccoli and colleagues have devised an alternative assessment method which uses the raw BIA measurements (i.e. Xc, R and PA) to generate clinical relevant outcomes. This method involves use of mathematical multivariate normal distribution and consists of plotting the impedance vector (Z) as a bivariate vector from its components (i.e. Xc, R and PA) on the Resistance-Reactance (RXc) graph, against a known distribution (bioelectrical impedance vector analysis – BIVA). BIVA will be further discussed in the next section of the thesis.

1.4.2 PRINCIPLES OF BIVA

Bioelectrical impedance vector analysis (BIVA), can be compared to the electrocardiogram, it uses graphical vectors to provide a visual analysis of BIA data. Using this method the impedance vector (Z) is plotted as a bivariate vector from its components, R (X axis) and Xc (Y axis), after being standardized by height (H); this forms two correlated normal random variables (i.e. a bivariate Gaussian vector). Elliptical probability regions of the mean vector can be plotted on the RXc plane forming elliptical probability regions on the RXc plane, which are tolerance ellipses for individual vectors and confidence ellipses for mean vectors.

1.4.3 THE RXC GRAPH METHOD IN CLINICAL BIO-IMPEDANCE: TOLERANCE ELLIPSES

Tolerance ellipses (also known as prediction ellipses, or iso-density probability ellipses, or confidence ellipses) are the bivariate reference intervals of a normal population for an observation. The RXc graph features three tolerance ellipses: the median, the third quartile, and the 95th percentile (i.e. 50%, 75% and 95% of individual points). This allows for more detailed analysis of vector position than the two (75% and 95%) originally used in the first article detailing the RXc graph.
method. This results in the development of a five-point scale by consideration of the upper and lower halves of tolerance ellipses that are greater than 50% (Figure 5 and 6). Formulas for the calculation of the bio-impedance confidence and tolerance ellipses are presented in Appendix 1.

**FIGURE 5: THE RXC GRAPH WITH 95%, 75% AND 50% TOLERANCE ELLIPSES (REPRODUCED WITH PERMISSION)**

![Image of RXC graph with tolerance ellipses]

**1.4.4 INTERPRETATION OF BIVA USING THE RXC GRAPH**

The statistical properties of the RXc graph allow the following analyses to be conducted:

1) Vector analysis of an individual subject at a defined moment in time (RXc point graph).
2) Evaluation of longitudinal body composition assessment through successive measurements in individual patients (RXc path graph - vector migration).
3) Evaluation of a group of subjects within a sample (RXc mean graph - confidence ellipse of a mean vector).\textsuperscript{150}

4) Comparison of BIVA patterns for different population groups based on data from previous studies (Z score graph).\textsuperscript{144}

1.4.4.1 INTERPRETATION OF INDIVIDUAL VECTOR POSITIONS: THE RXC POINT GRAPH

When assessing an individual, a point bivariate mean vector is placed on the reference RXc point graph (chosen from an appropriate reference population for the analysis). Plotting the two components R/H and Xc/H as an individual impedance vector (a point) on the RXc graph, allows for the distance from the reference mean vector to be ranked through the tolerance ellipses (RXc point graph). The point vector position can be evaluated to determine whether this lies within the 50%, 75% or 95% tolerance ellipses of the reference population.\textsuperscript{151} The tolerance ellipses can be used to divide the RXc graph into five sections which allows hydration status to be evaluated (Figure 6).

1.4.4.2 LONGITUDINAL BIO-IMPEDANCE ASSESSMENTS IN AN INDIVIDUAL OVER TIME: THE RXC PATH GRAPH (VECTOR MIGRATION)

Individual subjects can be followed up over time with successive bio-impedance readings. Repeated measurements are plotted successively on the RXc path graph to determine variation of the bio-impedance readings over time. Change in vector position is termed ‘vector migration’ and provides information of the characteristic change in body composition (Figure 7). This can be used to evaluate the clinical course of a condition, for example a weight loss programme or haemodialysis therapy (Figure 8).
FIGURE 6: RXC GRAPH DIVIDED INTO A 5-POINT SCALE ACCORDING TO 50th AND 75th PERCENTILE TOLERANCE ELLIPSES TO CLASSIFY HYDRATION STATUS

The RXC graph divided into a 5-point scale according to 50th and 75th percentile tolerance ellipses to classify hydration status. DYNAMIC STATE is depicted with ellipses ranging from 1 to 5, where 1 represents less fluids and 5 represents more fluids. The major axis is associated with tissue hydration, and the minor axis is associated with soft tissue mass.

FIGURE 7: BIVA PATTERNS FOR STEADY STATE AND VECTOR MIGRATION USING THE RXC GRAPH

A forward or backward displacement of vectors parallel to the major axis of ellipses was associated with dehydration or fluid overloading, respectively, reaching extremes out of the poles. Vectors above or below the major axis (meaning upper-left or lower-right half of ellipses) were associated with more or less cell mass in soft tissues, respectively, with extremes along the minor axis. Figure kindly supplied by the author.
FIGURE 8: IMPEDANCE VECTOR MIGRATION ASSOCIATED WITH HAEMODIALYSIS DEPICTED ON THE RXC GRAPH

Reference values for an individual vector (thin arrow to the centre of ellipses) are depicted as 50%, 75%, and 95% tolerance ellipses (male, Italian population). Solid circles represent vectors at the start and the end of the session. Open circles represent vectors after 30 (label a), 60 (label b), 120 minutes (label c), and in the next days, after 24 (label d), 48 (label e), and 68 hours (label f). The vector lengthening during the haemodialysis session is represented by the bold arrow in the direction of the major axis. The trajectory followed by vector shortening after dialysis is represented by segments of a path still parallel to the major axis of tolerance ellipses. Small, hatched ellipses represent the 95% confidence of the mean, pre (lower ellipse) to post (higher ellipse) dialysis vector displacement in a large Italian population. Reproduced with permission.

1.4.4.3 EVALUATION OF A GROUP OF SUBJECTS WITHIN A SAMPLE: THE RXC MEAN GRAPH (CONFIDENCE ELLIPSES FOR MEAN VECTORS)

Mean impedance vectors are useful for the evaluation of a group of subjects from a particular population (for example, advanced cancer patients). This vector is obtained from plotting the mean components of R/H and Xc/H on the RXc mean graph for all the subjects studied. This is an estimate of results that would be obtained if the total population (i.e. all patients with advanced cancer) were
studied. The 95% confidence ellipse of this vector, will establish the variability in the population and the likelihood the true value lies within the confidence ellipse. In vector analysis, two mean vectors with non-overlapping 95% confidence ellipses are considered significantly different (P<0.05); however, this is not always true vice versa (Figure 9). Significance testing can be further evaluated using the Hotelling’s $T^2$ tests (section 1.4.5).

**FIGURE 9: EXAMPLE OF RXC MEAN GRAPH ANALYSIS**

![Mean vectors of 95% confidence limits patients with cancer compared with controls. Abbreviations: CS =control subjects; LDD =cancer patients with locally advanced or disseminated disease; WD = cancer patients without disease. Reproduced with permission. 98](image)

1.4.4.4 COMPARISON OF BIVA DATA FROM PREVIOUS STUDIES

In statistics, a standard ‘z-score’ analysis can used to compare a measurement to a reference value or population. The ‘z-score’ is the number of standard deviations away from the mean value of the reference group. Z-scores provide information about the individual score relative to others in the distribution. A clinical example of the ‘z-score’ is the standardisation of the differing units reported by bone density machines to facilitate the calculation of bone fracture risk. Similarly, ‘z-scores’
can be used with BIVA to facilitate standardisation for the different types of bio-impedance assessments and analysers. This is because the relationship between Xc and R is a reflection of the different electrical properties of tissues that are affected in various ways by disease, nutritional status and hydration status.\textsuperscript{93} Therefore, transformation of these measurements to ‘z-scores’ to facilitate comparisons between different conditions and diseases (from different studies) provided each population is evaluated directly against its reference population (Figure 10).\textsuperscript{144}
FIGURE 10: DATA DRAWN FROM THE LITERATURE AND PLOTTED ON THE RXC-SCORE GRAPH AFTER TRANSFORMATION OF THE IMPEDANCE MEASUREMENTS FROM SEVERAL DISEASE GROUPS INTO BIVARIATE ‘Z-SCORES’ (WITH RESPECT TO THEIR REFERENCE POPULATION).

Solid and open circles represent male and female, respectively. A forward or backward displacement of vectors parallel to the major axis of ellipses was associated with dehydration or fluid overloading, respectively, reaching extremes out of the poles. Single score vectors are from athletes, obese subjects of class I to III or patients with chronic renal failure in conservative treatment, nephrotic syndrome (oedema), lung cancer, acquired immunodeficiency syndrome in stages WR 3 to 5 or WR 6, and anorexia nervosa. Repeated score vectors are from climbers before and after high altitude dehydration, haemodialysis patients, either lean or obese, before and after fluid removal with a dialysis session, and dehydrated patients with cholera before and after fluid infusion. Vectors above or below the major axis (meaning upper left or lower right half of ellipses) were associated with more or less cell mass in soft tissues, respectively, with extremes along the minor axis. Abbreviations: CRF = chronic renal failure; HD= haemodialysis; HDo= obese haemodialysis patients; HIV= human immunodeficiency virus stages 1-6; Ob/1-3= obese subjects of classes I to III; WR= Walter Reed stages 1-6. Reproduced with permission.
1.4.5 STATISTICAL TESTS FOR THE RXC GRAPH
The statistical tests used to analyse the RXc graph are outlined below.

1.4.5.1 HOTELLING’S TWO-SAMPLE T² TEST STATISTIC
The Hotelling’s two-sample T² statistic is a multivariate extension of Student’s t test for unpaired data to compare mean vectors from two groups. This assumes that data is normally distributed but is robust against departures from normality.¹⁵¹

1.4.5.2 HOTELLING’S PAIRED ONE-SAMPLE T² TEST
The Hotelling’s paired one-sample T² test is a multivariate extension of the Student’s t test for paired data in comparison of mean difference in vectors in one sample only. This is useful for determining difference in vectors on repeated measurements in the same subject. This test assesses vector displacement of confidence ellipse from the origin (i.e. 0,0 on the RXc graph). A 95% confidence ellipse crossing the origin is not statistically significant.¹⁵¹

1.4.5.3 MAHALANOBIS GENERALISED DISTANCE (D)
Both of the Hotelling’s tests utilise functions of Mahalanobis' generalised distance (D), a statistical method to discriminate between groups by accounting for the variance of each variable and the covariance between variables. In this case, D uses vector variation to compare differences between means within groups.¹⁵¹

1.4.6 CLINICAL APPLICATION OF BIA AND BIVA
The relationship between Xc and R is a reflection of the different electrical properties of tissues that are affected in various ways by disease, nutritional status and hydration status.³³ Measurement using BIA provides a simple, non-invasive method of obtaining assessment of body composition states. The BIA instrument consists of a small portable device, which is robust and relatively low cost in comparison to other assessment methods which are impractical in routine clinical practice.⁷⁶ BIA provides estimates of fat-free mass, body fat, body cell mass, total body water, extracellular water and intracellular water. Consequently, BIA has been
used in a wide range of settings and populations (for example sports medicine, paediatrics, renal medicine and the elderly).

Specifically, impedance analysis has been used for assessments of hydration, malnutrition and rehabilitation, metabolism, prognosis and disease assessment. BIA equipment is commercially available, affordable and has been incorporated into standard health equipment, such as home weighing scales and exercise machines, thus providing the ability to use BIA measurements for health-related outcomes.

The European Society for Clinical Nutrition and Metabolism (ESPEN) has outlined the role and methodological requirements of BIA in clinical practice for a wide variety of populations and disease groups.

As previously discussed, BIA uses simple or multiple regression equations to make predictions of masses and volumes of body compartments in subjects with fixed and normal 73% hydration of soft tissues. However, impedance measurements may be inaccurate in situations where these presumptions are not met, for example, in abnormal hydration conditions. Additionally, the standard error of the estimate of the best BIA regression equations is large (95% prediction interval greater than ± 3 kg or L) which may limit its use in clinical practice.

Consequently, Piccoli and colleagues devised an alternative assessment method which uses the raw BIA measurements (i.e. Xc, R and PA) to generate clinical relevant outcomes. As these methods are independent of regression equations they are able to provide accurate assessments in individuals who fail to meet presumptions of standard prediction equations. Firstly, phase angle (PA) has been utilised as a prognostic marker in various patient groups, including: Human Immunodeficiency Virus (HIV), dialysis patients, breast cancer, lung cancer, colorectal cancer, mixed advanced cancer and pancreatic cancer. In these studies, a lower phase angle is associated with worse prognosis.

PA has been found to be a sensitive indicator of overall health with a high correlation found between PA and other comorbidities. In lung cancer, the PA was closely associated with tumour volume. Lower PA was associated with increased fatigue and poorer muscle endurance in advanced cancer patients. In
one study, a PA value less than the 5th percentile was found to be an independent predictor for impaired nutritional status, poor physical function and shorter survival in cancer patients.\textsuperscript{194} PA is reduced in haemodialysis patients and those with renal transplants when compared to normal populations.\textsuperscript{175,195} In HIV, PA is linked to disease severity, with lower values significantly correlated to worse disease.\textsuperscript{196-198}

PA has shown significant inverse correlation with nutrition markers, such as pre-albumin and albumin.\textsuperscript{183,184} Additionally, PA has been found to be significantly lower in malnourished children, and showed a good correlation with other anthropometric measures.\textsuperscript{167} Furthermore, PA shows linear correlation with items of the subjective global assessment (SGA) tool, a malnutrition identification tool, with lower phase angles observable in severely malnourished patients.\textsuperscript{165,199}

Overall, the literature illustrates how PA appears to relate to morbidity and mortality in several clinical conditions, but there is a lack of standardized cut-off values for comparison. Future studies may also show its usefulness in monitoring nutritional interventions. By way of contrast there is a lack of data from cancer populations.\textsuperscript{105} Cancer (and other wasting diseases) reduces ICW through cachexia, such that the TBW derived from equations for normal populations will become less accurate.\textsuperscript{200}

The advantage of BIVA is that it allows information to be obtained simultaneously about changes in tissue hydration or soft-tissue mass, independent of regression equations, or body weight. This allows for accurate interpretation of BIVA readings even if patients are at extremes of weight or volume distribution. When the R and Xc are plotted graphically after standardising for height, different disease/conditions appear to form distinct clusters (figure 10). Consequently, BIVA measurements can be compared with reference populations to enable comparisons with healthy populations and other diseases.\textsuperscript{144} BIVA has been used to study hydration in a variety of different diseases (e.g. renal failure, cholera, congestive cardiac failure),\textsuperscript{95,98,158,163,201-205} and to undertake general body composition assessments in lung cancer\textsuperscript{98,158} and cancers of the head and neck.\textsuperscript{206} These studies provide many examples of how BIVA has been used to facilitate comparisons in
patients using the features of the RXc graph. Changes in the shape and direction of
plotted vectors (vector migration) on repeated measurements in the same
individual allow change in hydration status over time to be recorded.\textsuperscript{103, 150} BIVA has
been used in this way to assess longitudinal change in hydration in oedematous
patients receiving haemodialysis.\textsuperscript{150, 173} However, it is important to note that
although BIVA is capable of detecting fluid imbalances it is unable to quantify actual
fluid volumes of compartments.\textsuperscript{207}
SECTION 5: HYDRATION IN CANCER

1.5.1 INTRODUCTION TO THE SYSTEMATIC LITERATURE REVIEW

A systematic literature review of the clinical methods of assessing hydration in advanced cancer (physical examination, symptom assessment and biochemical measures) is presented in this section of the thesis. In addition, this review will critically appraise the evidence about dehydration-related symptoms that are associated with advanced cancer. BIA was evaluated to examine its potential use in the assessment of hydration. The section concludes with a discussion of the possibilities for future research based on the strengths and limitations of the evidence base.

This systematic review has helped to inform the development of this study. A preliminary version of this review was published in the Journal of Pain and Symptom Management. This thesis will further build on this literature, using the published systematic review as a basis. This text has been modified for production in this thesis with permission from the publisher. The literature was searched between August 2012 and December 2013. Four electronic databases were searched (Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trails and Scopus) using combinations of the keywords which were combined in a systematic fashion (Table 1). The search was limited to English language literature published between 1960 – 2013. The search strategy for Medline is shown in Table 1 and was adapted for other databases.
TABLE 1: SEARCH STRATEGY APPLIED TO RECEIVE PAPERS FROM MEDLINE

<table>
<thead>
<tr>
<th>Query number</th>
<th>Query content</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>(((palliative care) OR hospice) OR terminally ill) OR terminal care</td>
</tr>
<tr>
<td>#2</td>
<td>(((cancer) OR neoplasms) OR tumour) OR carcinoma) OR malignancy</td>
</tr>
<tr>
<td>#3</td>
<td>dehydration</td>
</tr>
<tr>
<td>#4</td>
<td>(water-electrolyte balance) OR fluid balance</td>
</tr>
<tr>
<td>#5</td>
<td>bioelectrical impedance</td>
</tr>
<tr>
<td>#6</td>
<td>#1 AND #2</td>
</tr>
<tr>
<td>#7</td>
<td>#3 OR #4</td>
</tr>
<tr>
<td>#8</td>
<td>#5 AND #6</td>
</tr>
<tr>
<td>#9</td>
<td>#6 AND #7</td>
</tr>
<tr>
<td>#10</td>
<td>#8 OR #9</td>
</tr>
<tr>
<td>#11</td>
<td>Limit #10 to Humans and English language</td>
</tr>
</tbody>
</table>

Bibliographies of relevant articles were manually searched to identify further articles for potential inclusion. Additionally, a hand search of the most recent issues (January 2010 to December 2013) of 12 relevant peer-reviewed journals was conducted (Table 2).

TABLE 2: PEER REVIEWED JOURNALS SEARCHED AS PART OF REVIEW OF LITERATURE

<table>
<thead>
<tr>
<th>Journal of Pain and Symptom Management</th>
<th>BMJ Supportive and Palliative Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal of Palliative Care</td>
<td>Journal of the American Medical Association (JAMA),</td>
</tr>
<tr>
<td>Palliative Medicine</td>
<td>Annals of Internal Medicine</td>
</tr>
<tr>
<td>Journal of Palliative Medicine</td>
<td>Lancet Oncology</td>
</tr>
<tr>
<td>New England Journal of Medicine</td>
<td>Nutrition</td>
</tr>
</tbody>
</table>
Abstract data from five conferences was searched; this consisted of abstracts from the previous three years (2000 – 2013) published in the American Academy of Hospice and Palliative Medicine (AAHPM) conference, the European Association of Palliative Care (EAPC) conference, the Palliative Care Congress, the International Congress of Palliative Care and the Marie Curie Research Conference. In order to obtain further information about the grey literature abstracts, which were selected for inclusion in this study, the authors of these studies were contacted and asked to provide more information about the research in question. Further details of studies included in this review are presented in the Appendix 2.

1.5.2 SELECTION CRITERIA

The selection process for articles in the review is described in this section. A stepwise procedure was used to identify relevant studies. Studies addressing hydration assessment (physical examination, biochemical measures, symptom assessment, and bioelectrical impedance) in advanced cancer patients were eligible for inclusion in the review. For the purposes of this review, advanced cancer was defined as; a diagnosis of cancer where no further curative treatment is possible, which may be associated with metastases (histological or radiological). Articles were excluded if the studies were not in English or primarily reported paediatric populations.

1.5.3 RESULTS

Results of the literature search are summarised in Figure 11. The initial literature search using the keywords outlined in the Methods section returned 338 articles. A total of 316 of these articles were rejected after the review of the abstract as not relevant. The remaining 22 articles were examined by our inclusion and exclusion criteria. Three articles were excluded as they primarily reported non-cancer populations, resulting in the inclusion of 19 studies in the review. Details of the included studies are presented in appendix 2.
FIGURE 11: OVERALL SELECTION PROCESS FOR STUDIES INCLUDED IN THE REVIEW

Records identified through database searching
- Medline (n=88)
- Scopus (n=291)
- Cochrane register of controlled trial databases (n=1)

Additional records identified through searching reference lists of selected articles (n=43)

Potentially relevant articles after duplicates removed (n=338)

Studies selected for full-text review (n=22)

Studies included in review (n=19)

Excluded (n=316)
- Review articles
- Non-clinical outcomes
- Commentaries, letters to the editor, news updates

Excluded (n=3)
- Non-cancer
1.5.4 DEHYDRATION DEFINITIONS AND PHYSIOLOGY IN CANCER

Cancer is defined as an uncontrolled proliferation of cells that express varying degrees of fidelity to their precursors.\textsuperscript{208} Physiologically, dehydration has been defined as total body water (TBW) deficit, which is predominantly intracellular.\textsuperscript{209} This process is associated with hypernatraemia; with elevated serum osmolarity, which in turn stimulates the sensation of thirst from the thirst centre.\textsuperscript{210} This pattern may not be observable in advanced cancer, due to differences in fluid requirements and disease pathophysiology, when compared to non-cancer populations.\textsuperscript{200,211} In cancer, intracellular dehydration is associated with proteolysis and cachexia\textsuperscript{212,213} and leads to an increase in antidiuretic hormone (ADH) through stimulation of osmoreceptors or from direct release from the tumour.\textsuperscript{214,215} Furthermore, weight loss, decreased renal perfusion and cachexia are associated with a loss of intracellular water and solutes affecting hypothalamic osmoreceptors, which in turn stimulates ADH release.\textsuperscript{216} ADH increases the water permeability of the distal tubule and collecting duct in the kidney, promoting water absorption and the maintenance of serum osmolarity and sodium at subnormal levels. Consequently, an abnormally low osmolarity may cause symptoms such as nausea, and confusion, which have been associated with dehydration.\textsuperscript{211}

In advanced cancer, hyponatremia is more common than hypernatremia.\textsuperscript{200,210} Hyponatremia results from sodium loss in excess of water, resulting in a low sodium and serum osmolarity.\textsuperscript{210} Medications such as selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs) are associated with hyponatremia and are frequently given to cancer patients for symptom management.\textsuperscript{217,218}

Dying cancer patients may achieve adequate hydration with much lower volumes of water than that are recommended for the average medical and surgical patient.\textsuperscript{211} This is likely to result from differences in body composition, such as a lower body weight due to cachexia and decreased clearance of free water caused by a variety of mechanisms. For example, patients with advanced cancer may have reduced insensible water losses due to a reduction in their physical activity. As hydration
studies are generally based on non-cancer populations, the subsequent research findings may not extrapolate to cancer patients. As a consequence, definitions of cancer dehydration vary throughout literature, with authors using different combinations of clinical parameters as diagnostic criteria. The lack of uniformity in definitions complicates study comparisons and makes decisions regarding the use of CAH difficult for clinicians. There is a need for further study in this area to address the limited research base.

1.5.5 PHYSICAL EXAMINATION AND SIGNS OF DEHYDRATION

Dehydration predominantly describes an intracellular process; however, the clinical assessment of hydration, through the process of physical examination, is a measure of the extracellular fluid compartment (i.e. extracellular water content (ECW); skin turgor, jugular venous pressure (JVP) and pulse). Consequently, clinical assessment is unable to diagnose intracellular dehydration. There are no routine bedside technologies that measure fluid in the intracellular space. Authors have attempted to address the issue by differentiating dehydration defined physiologically, from that derived from subjective clinical assessment. Consequently, the term clinical dehydration is used to include all types of fluid deficit as they appear in the clinical setting. Therefore, conflict exists between the clinical experience of dehydration, compared to the biochemical and physiological definitions of dehydration commonly found in the literature.

Non-cancer studies have found certain variables to correlate with dehydration (defined clinically and biochemically) in elderly populations, these include: tongue dryness, longitudinal tongue furrows, dry mucous membranes, upper body muscle weakness, confusion, speech difficulty, sunken eyes, dry axilla, a fall in systolic blood pressure, decreased sternal skin turgor and low body mass index (BMI). Based on the outcomes of these studies, Morita et al developed a dehydration score consisting of three variables (dryness of oral mucous membranes, axillary moisture and sunkenness of eyes) for use in cancer patients. This score was used to assess dehydration (in addition to assessments of delirium and peripheral oedema) in a study evaluating the association between CAH volume and symptoms in
terminally ill cancer patients with abdominal malignancies. Dehydration scores were significantly lower in the patients receiving CAH in the last 3 weeks of life compared to the non-CAH group; however, use of CAH was associated with increases in peripheral oedema. No significant difference in hyperactive delirium, communication capacity, bronchial secretions, agitation, myoclonus or serum biochemistry was evident between the two groups. A similar study, by the same author, studied the relationship between laboratory findings, artificial fluids, fluid balance and clinical measures of dehydration in terminally ill patients with abdominal cancer. The authors found no statistically significant difference in the fluid balance in patients with an increased clinical dehydration score compared to those without. Bruera and colleagues conducted a randomised controlled double blind trial involving dehydrated cancer patients receiving CAH. The authors found that myoclonus and sedation were reported less in the CAH group compared to placebo. However, these findings were not reproducible in a follow-up study by the same author or in a study by Morita et al which evaluated communication capacity and myoclonus as outcomes for cancer patients receiving CAH.

There is conflict over the accuracy of physical findings in the assessment of hydration in advanced cancer. Skin turgor has been shown to poorly correlate with fluid deficit and clinical dehydration as cancer patients are prone to changes in subcutaneous tissue which may create inaccuracy in its interpretation. Postural hypotension is identified as a feature of hypovolaemia (low blood volume), but lacks sensitivity as a test for dehydration. This highlights how different definitions of dehydration may create difficulty in interpreting study outcomes. Furthermore, postural hypotension may not be suitable in assessing some advanced cancer patients who are at risk of poor mobility, falls and taking medications known to cause hypotension, e.g. opioids and diuretics. Variations in body mass caused by cachexia and oedema may make BMI measurements unsuitable. Although part of a standard medical examination, capillary refill is only able to detect hypovolaemia in children and lacks sensitivity in adults.
1.5.6 BIOCHEMICAL MEASURES OF HYDRATION IN CANCER

Biochemical tests include the analysis of blood (obtained from venepuncture) and urine samples. A change in urine and blood chemistry provides clues to the underlying cause of hydration disturbances and helps the clinician identify potential treatments. Measures such as serum urea:creatinine ratio and urine:plasma osmolality ratio have been used to assess hydration status with ratios of ≥100 (mmol/mmol) and ≥1.2 respectively suggesting dehydration.\(^{209,210,219,241,242}\) Biochemical dehydration occurs when intracellular water is lost, leading to transmembrane water migration from the intravascular compartment under osmotic pressure and increased relative plasma sodium concentration.\(^{210,243,244}\) Electrolyte abnormalities, such as hyperkalaemia may suggest underlying causative factors of dehydration and may be useful prognostic indicators.\(^{245}\) Atrial naturietic peptide (ANP) level <15pg/ml has been used to define dehydration in palliative patients;\(^{246}\) however, the validity and reliability of this measure has not yet been determined. Observational studies have found that biochemical measures of dehydration poorly correlate with symptoms, such as thirst and dry mouth.\(^{247}\)

Biochemical investigations are performed for various reasons, including clinical monitoring in advance of medical procedures and assessment in response to change in the clinical condition of a patient. In these circumstances, abnormal renal function may prompt the clinician to consider the initiation of CAH; however, studies have shown that patients with advanced cancer may be prone to renal impairment at the end-of-life. The prevalence of pre-renal failure in cancer inpatients was 44% (n=27/62) in a study by Guo et al;\(^{248}\) no difference in length of stay was evident between patients with renal failure compared to those with normal renal function. Biochemical measures alone may not be able to detect clinically meaningful hydration changes in cancer patients, especially if measurements are performed without a record of the patient’s baseline renal function for comparison. Authors have demonstrated worsening renal function in cancer patients approaching death, irrespective whether CAH is administered or not.\(^{227,228,249}\) Therefore, in advanced cancer, static abnormal renal function
measurements may provide incomplete assessments of hydration status. A prospective study by Waller and colleagues examining hydration indicators in patients found 87% (n= 59/68) of dying patients were biochemically dehydrated. No difference in serum biochemistry or consciousness was found between patients receiving intravenous fluids compared to those who received no fluids. The authors concluded there was no clinical benefit to the administration of intravenous fluids in terminally ill cancer patients.

1.5.7 SYMPTOMS OF DEHYDRATION

Previous research has attempted to determine if symptom burden is related to dehydration and, consequently, whether the use of CAH improves these symptoms. The first quantitative estimate of dehydration symptoms in advanced cancer was conducted by Burge et al in 1993. This study involved a cross-sectional analysis of dehydration symptoms of 52 palliative cancer patients. A series of 100mm visual analogue scores (VAS) were used to evaluate the severity of seven symptoms (thirst, dry mouth, bad taste, nausea, pleasure in drinking, fatigue and pain) experienced by patients. Fatigue was the most severe symptom (65% rated greater than 50mm); dry mouth and thirst were also very prevalent (53.8% and 60% rated greater than 50mm respectively). The study found no association between symptom severity and fluid intake or between biochemical measures and thirst, a finding consistent with other studies.

Cerchietti et al demonstrated improvements in thirst and chronic nausea in symptomatic palliative cancer patients with limited oral intake, randomised to receive either CAH or standard medical therapy. Significant improvements in relief of thirst and chronic nausea were present in both groups at 24 hours; however, this effect was only maintained in the hydration group at 48 hours. Studies assessing oral symptoms and dehydration have found mixed results. Dry mouth and thirst were highly prevalent in a study of 82 palliative cancer patients at risk of dehydration. Of the 23 (28%) patients able to respond to the questions, 20 (87%) reported dry mouth and 19 (83%) complained of thirst. No association between thirst, dry mouth, respiratory tract secretions and biochemical dehydration was
found. Similarly, in a cohort of 88 palliative patients, Morita et al\textsuperscript{246} found thirst to be highly prevalent, but poorly associated with dehydration. Interestingly, the authors found thirst was associated with water depletion (defined by atrial natriuretic peptide). However, a lack of validity and reliability of ANP and the arbitrary cut-off level defined by the authors may indicate this area requires further study before definitive conclusions are drawn.

Several studies have found no association between CAH and symptoms. Musgrave et al\textsuperscript{252} evaluated the effect of CAH on the sensation of thirst in 30 terminal cancer patients. Nineteen patients were able to communicate thirst intensity, but no association between level of thirst, intravenous fluids and biochemical parameters was demonstrated. Similarly, Yamaguchi et al,\textsuperscript{253} in a multicentre prospective observational study of 161 advanced cancer patients receiving CAH, found no significant difference in symptomatic burden between patients receiving high volumes (>1litre/24hours) compared to those receiving lower fluid volumes (<1litre/24hours). Additionally, Bruera et al\textsuperscript{230} found no statistically significant difference in symptoms, quality of life or survival between patients receiving 1000mls of 0.9% saline daily compared to placebo (100mls daily) in 129 cancer patients recruited from six hospices. There is little evidence to support the role of CAH in the management of delirium in advanced cancer.\textsuperscript{254,255} A statistical analysis of hospital inpatient data, of 1125 advanced cancer patients, failed to demonstrate a relationship between hydration and delirium;\textsuperscript{256} this is a similar finding in other studies.\textsuperscript{227,251,253} However, hyperactive delirium was found to be more prevalent in patients with advanced abdominal cancers, receiving small volumes of CAH (<1litre/day), compared to patients receiving larger volumes (>1litre/day).\textsuperscript{253}

Previous studies have highlighted the potential that CAH may cause adverse effects in dying patients. Nakajima et al\textsuperscript{257} explored the influence of hydration on symptoms in a series of 75 patients with advanced abdominal cancer. The study found CAH improved oral membranous signs of dehydration but worsened peripheral oedema, ascites and chest secretions. Recently, Fritzson et al\textsuperscript{258} reported an association between dyspnoea and intravenous fluids in a retrospective analysis of 251 hospice inpatients receiving end-of-life care. Patients had a variety of
diagnoses with cancer most prevalent (n=194; 77.3%). Compared to controls, higher dyspnoea scores were reported for patients receiving larger CAH volumes administrated in the last 24 hours and seven days of life.

**1.5.8 USE OF BIA AND BIVA IN ADVANCED CANCER**

The clinical application of bio-impedance methods is discussed in section 1.4.6. The characteristics of bio-impedance analysis (e.g. portable and non-invasive) are favourable for the study of hydration in advanced cancer. Previous studies have used the technology to evaluate hydration in advanced cancer. Simons et al\textsuperscript{83} evaluated the applicability of BIA to predict TBW (deuterium dilution, $\Delta$-TBW\textsubscript{deu}) in 16 underweight and 25 normal weight cancer patients. The authors found that although $H^2/R$ was a strong predictor of $\Delta$-TBW\textsubscript{deu}, the use of prediction equations overestimated $\Delta$-TBW\textsubscript{deu} in underweight patients. The authors conducted a further study in 33 cancer patients using BIA to compare changes in $H^2/R$ correlated with changes in $\Delta$-TBW\textsubscript{deu} over a 12 week period.\textsuperscript{136} Changes in $\Delta$-TBW\textsubscript{deu} occurred in both directions (mean +0.2 +/- 1.6 L, range -3.3 to +3.1 L) and were significantly predicted by changes in $H^2/R$ ($r^2 = 0.43$, $P < 0.0001$, SEE = 1.22 L), although precision was poor (residual SD = 1.2 L). The authors conclude that in underweight and normal-weight cancer patients, BIA-derived changes in $H^2/R$ significantly predict changes in total body water assessed by deuterium dilution.

Recently, Davis et al\textsuperscript{200} performed a prospective observational study, using BIA, in patients with advanced cancer receiving CAH. BIA was done for 3 consecutive days from initiation of CAH. The authors found that a greater PA on day 1 of CAH predicted better survival; however, a rise in PA (indicating increased reactance and the distribution of fluid to the intracellular compartment) during CAH predicted shorter survival. The authors propose that an increase in PA during CAH reflects pre-existing intracellular dehydration, which occurs in patients who are more likely to have cachexia-anorexia syndrome, and hence, a worse prognosis compared to those without a PA rise during CAH. This may suggest that PA may be able to assist in prognostication and may highlight underlying physiological differences between cancer patients receiving CAH. Crawford et al\textsuperscript{259} used BIS to show that elevated
metabolic rate and accumulation of body fluids were indicators of poor prognosis in a series of palliative cancer patients. Although interesting, these recent studies focus on survival and do not explore issues regarding hydration assessment or the appropriateness of using CAH in these patients. To date, BIVA has yet to be used to specifically assess hydration in advanced cancer. Consequently, BIVA may provide a way to assess and monitor change in hydration over time in advanced cancer patients.

### 1.5.9 MAIN FINDINGS OF THE REVIEW

Clinical examination and biochemical tests are standard methods of assessing hydration, but limitations exist with these methods in advanced cancer. For example, physical examination has a low sensitivity and specificity for identifying fluid deficit. Study outcomes are often conflicting and many variables lack evidence for their inclusion in assessing hydration status in adult cancer patients. Historically, evidence regarding hydration assessment originates from studies in non-cancer populations and particular components of a physical examination (e.g. capillary refill, skin turgor) appear to have less significance in advanced cancer. Equally, there is disagreement about the most appropriate biochemical tests and the diagnostic criteria to determine biochemical dehydration. The differences between local, national and international definitions of dehydration may cause clinicians to be unsure about the significance of biochemical results in advanced cancer patients.

BIA is able to assess body composition and has been used as a prognostic marker in cancer studies. One study demonstrated PA increase in patients receiving CAH was associated with increased mortality. This may suggest cancer patients differ physiologically in their ability to handle fluids, with some more prone to adverse effects than others. The study is limited by small numbers of patients and a lack of standardisation of the type of fluid prescribed and the rate of volume replacement. If a true difference exists this may highlight the importance for clinicians to consider these factors when administering CAH. Furthermore, studies using bioelectrical impedance may potentially be a tool to enable clinicians to
better understand hydration in advanced cancer. BIA alone is limited in its ability to assess hydration in advanced cancer;\textsuperscript{103} however, interpretation using a vector analysis (BIVA), improves the accuracy of measuring static and dynamic hydration states.\textsuperscript{144,201,202} The non-invasive nature of the technology may be popular for researchers keen to utilise novel methodologies for assessing hydration in advanced cancer. Consequently, BIVA shows promise as a method for assessing hydration and could be potentially used to further scientific study into the relationship between hydration and related symptoms. However, further study is required to establish whether measurements of fluid distribution in advanced cancer, as determined by BIA and BIVA, are clinically relevant.

Several factors limit the viability of clinical and biochemical assessment techniques. For example, the elderly (which comprise the majority of cancer patients) may have abnormal biochemical profiles secondary to non-hydration related factors, such as altered muscle mass and pre-existing renal or metabolic conditions.\textsuperscript{211} Repeated venepuncture may cause pain, discomfort and be viewed as inappropriate for use, in the assessment of cancer patients, in certain circumstances (for example, in the dying phase).\textsuperscript{261,262} Consequently, clinicians may avoid performing venepuncture in situations where the risks of causing harm may outweigh the benefits of obtaining biochemical tests. In this review, we highlighted the concept of clinical dehydration defined by bedside physician assessment. Clinicians may argue that there is little utility in identifying biochemical dehydration in a patient without symptoms, hence, only clinically relevant signs and symptoms of (de)hydration will be managed; however, in this population, there is a lack of agreement of which signs and symptoms are clinically relevant. Additionally, without an understanding of the pathophysiology of disease and its resultant symptoms there is a risk that features of dehydration may be inaccurately interpreted and hence, inappropriately managed. Therefore, it is important for dehydration in cancer to be appropriately defined to enable associated signs and symptoms to be identified, thus allowing appropriate management to be initiated. For example, various symptoms have been used as indicators for dehydration, but there is disagreement about the accuracy of these. There is some evidence to suggest that nausea is improved
through the administration of CAH. However, the association of nausea with hydration (and other variables) has not been clarified. Despite a high prevalence of fatigue, the use of CAH does not appear to improve this symptom in cancer patients. Dry mouth and thirst are common in cancer; however, these variables may be unreliable indicators of (de)hydration due to their association with other factors. One study suggests the significance of thirst when serum ANP is used to define dehydration, but the validity and reliability of this measure has not yet been determined. Despite a greater prevalence of hyperactive delirium in patients receiving reduced volumes of CAH compared to larger volumes, the evidence is poor for the influence of hydration on delirium in advanced cancer. Overall there is a lack of clinical assessment tools to evaluate hydration in advanced cancer, and unclear data about which symptoms are most related to dehydration. These findings, combined with the unclear benefits and burdens of CAH, make decisions about the use of CAH challenging for healthcare professionals.

### 1.5.10 WHAT THIS REVIEW ADDS

This review is unique in highlighting the potential of BIVA to assess hydration in advanced cancer patients. We have identified a lack of evidence relating to the assessment and symptomatic treatment of dehydration in cancer; a finding consistent with similar studies in this area.

### 1.5.11 LIMITATIONS

We recognise there are several limitations with this review. Although hand searching of relevant journals and grey literature took place, this was limited to the past 3 years and the abstract lists were unavailable for some conferences; consequently, there is the potential that data was excluded from this review. Although a structured process for identification and inclusion of articles was adopted, the reviewers were not blinded to the authors and institutions of the reviewed articles. Consequently, there is risk of the reviewers’ own bias relating to articles included or excluded from the review. Many of the included studies were small, descriptive, under-powered studies with differing definitions of dehydration.
These diagnostic definitions may have been based on biochemical criteria, clinical markers or a combination of both; therefore, comparisons between the studies are difficult. Studies involving patients with advanced cancer present ethical and methodological challenges that are compounded by the difficult issue of (de)hydration. It can be argued that researchers and ethics committees are still learning about suitable approaches for this subject, which will limit the number of high quality research studies. BIA and BIVA has been used to assess body composition in several populations; however, there is a lack of studies using this technology to report on clinically relevant outcomes (for example, symptoms burden, survival and the effect of CAH on these parameters) in advanced cancer. Additionally, we were unable to identify any literature reporting on the use of BIVA to evaluate hydration in advanced cancer. The intervention studies involving CAH used various routes of administration, different fluid preparations, over differing time periods at different stages of the subjects’ illness. Although the outcomes of these studies are interesting, the lack of harmony between methodology and outcomes limits the ability of this review to synthesise data.

A lack of consensus of how to assess hydration in advanced cancer makes decisions regarding the use of CAH difficult for the clinician. Further complexity is added due to the limited number of high quality studies assessing the benefits and burdens of CAH for this population. This review has highlighted how advanced cancer patients may experience some benefits from receiving CAH, such as improvements in sedation, myoclonus and nausea. However, there is the potential to cause harm, in terms of worsening symptoms of fluid retention (e.g. dyspnoea, peripheral oedema, pleural effusion, ascites). On the basis of insufficient evidence, we are limited in our ability to draw definitive recommendations. Clinicians are therefore advised to make assessments based on the perceived benefits, risks and burdens to the individual. The clinician should be familiar with existing methods of hydration assessment and be aware of their limitations.

Currently, no studies have used BIVA for the assessment of hydration in advanced cancer patients. Pilot studies using BIVA are required to determine its feasibility and efficacy before conclusions can be draw. If feasible, BIVA may have a role in
evaluating hydration in advanced cancer and improving knowledge of hydration in
dying patients. BIVA could be used in combination with other hydration assessment
methods to determine the scientific association of symptoms with dehydration,
facilitating the creation of core-outcome measures for hydration, which can further
support intervention studies using CAH. Consequently, future studies could use BIA
and BIVA to determine its usefulness in predicting and monitoring clinical response
to treatments (such as CAH) and survival through static and longitudinal
assessments.

1.5.12 SUMMARY OF CHAPTER

There is a lack of evidence concerning the association of clinical symptoms and
physical signs with hydration states in advanced cancer. Additionally, there is a lack
of evidence concerning value of clinical interventions, such as CAH, in the
management of fluid-related states of advanced cancer.

This review highlights the potential value of BIVA, a validated method of assessing
body composition, in the assessment of hydration. BIVA shows promise as a
hydration assessment tool but requires further study in advanced cancer.
Innovative methodologies for research are required to add to the evidence base
and ultimately improve the care for the dying.
CHAPTER 2: MATERIALS AND METHODS

This chapter describes the technical processes that were necessary for the project to be conducted. Firstly, we begin with a description of the study population and the research setting. The chapter then outlines the research management and governance issues. The experimental design of the study is highlighted, through the outline of the methodology, data collection tools and the research schedule. The chapter concludes with presentation of the statistical analysis plan.

SECTION 1: DESCRIPTION OF THE STUDY POPULATION AND THE RESEARCH ENVIRONMENT

2.1 STUDY POPULATION

The study population for this project involved adults affected by advanced cancer receiving care in the Marie Curie Hospice Liverpool (MCHL). Advanced cancer was defined as a histological or radiological diagnosis of cancer which was incurable. Participants were recruited according to the following eligibility criteria.

2.1.2 ELIGIBILITY CRITERIA

The eligibility criteria for entry into the study are listed below:

2.1.2.1 INCLUSION CRITERIA

- Admitted to the Marie Curie Hospice Liverpool (MCHL) from December 2013 onwards.
- Aged 18 years or above.
- Known diagnosis of cancer (proven by histology or radiological imaging).
- No further curative treatment possible.
- Able to understand and communicate in English (this may be through the use of communication aides and/or interpreter).

- Serum urea and creatinine recorded by the clinical team in the previous 72 hours.

2.1.2.2 EXCLUSION CRITERIA

- Patients with implantable defibrillator devices.

- Patients unable to provide fully informed consent.

- Active transmissible infections (including, Methicillin-resistant Staphylococcus aureus (MRSA), Clostridium Difficile Toxin (CDT) and Norovirus infections).

- Receiving clinically assisted hydration (CAH) at time of assessment.

- Currently receiving antineoplastic treatment.

Participants were enrolled to the study providing they met the above eligibility criteria and were able to provide informed consent. BIA is safe, non-invasive with no history of adverse events. The use of BIA is not recommended in patients with implantable pacemakers as these devices are untested with the BIA technology. Only subjects who were able to provide full consent (with understanding of the reason for participation in the study and the potential risks and benefits) were included. Every effort was made to accommodate patients unable to communicate orally in English within the study, through individual assessment of the need for communication support for each participant. Patients with active transmissible infections were excluded, due to the risk of contamination of the research equipment resulting in subsequent transmission to other participants. These individuals would be eligible to participation once they were free of infection and deemed suitable (and able) to participate by the clinical team.

All study participants were receiving specialised palliative care but were not necessarily at the end of their lives. All participants were free from antineoplastic
treatment and were not receiving clinically assisted nutrition or hydration at the
time of assessment.

2.1.3 DESCRIPTION OF THE RESEARCH SETTING

The MCHL is a 30 bedded specialist palliative care unit situated in North West
England and provides inpatient, outpatient and day care services. Specialist
palliative care is provided for a broad range of palliative problems for a
predominantly Caucasian population of approximately 890,971. Patients are
admitted directly from community and/or hospital settings. Inpatients are reviewed
daily by the medical team, which is led by a consultant in palliative medicine. All
patients receive individualised supportive therapies and, if necessary, medical
interventions. The hospice mainly cares for metastatic cancer patients (of various
subtypes) but also cares for non-cancer patients (prevalence approximately 66% vs.
34% respectively). Approximately, the length of stay for patients is two weeks;
60% of patients are discharged, either to their own home or an alternative care
facility. In the calendar year of 2012, the MCHL received 853 unique referrals for
either inpatient, outpatient or day therapy care services. This included 740
inpatient admissions (comprising of 387 patients) and 259 (67%) deaths.

The MCHL is integrated with the Marie Curie Palliative Care Institute Liverpool
(MCPCIL), a partnership comprising of the MCHL, the University of Liverpool and
the Royal Liverpool University and Broadgreen NHS Hospitals Trust. This
relationship helped facilitate the development of the research infrastructure, which
was necessary to conduct the study.
2.1.4 DEVELOPMENT OF A RESEARCH INFRASTRUCTURE IN THE HOSPICE SETTING

Several factors create difficulties when attempting to conduct a research project with a hospice. This includes a lack of a research infrastructure within the institution, limited research personnel and, importantly, the absence of an overseeing research governance structure. Consequently, a formal plan to develop a research structure in the hospice was undertaken as part of this study, in order to facilitate the conduct of this research (and proposed future work) within the hospice setting. The research infrastructure involved the development of the following:

Staff involvement

A series of meetings were held with members of the multi-disciplinary teams providing care for patients in the hospice. These meetings provided the researcher with an opportunity to meet with staff members to introduce himself and the project, whilst providing explanations of the methodology, protocol and practical demonstrations of the equipment.

Research in the Hospice

Prior to commencement of the study, posters advertising the study (appendix 3) were placed on notice boards throughout the hospice. A factsheet was developed to provide healthcare professionals with a summary of the proposed study (appendix 4); this was distributed during multidisciplinary research seminars. Additionally, research support folders (containing the healthcare professional factsheet, participant information sheets, examples of data collection sheets, and the published systematic review by Nwosu et al\textsuperscript{105}) were created and placed in the clinical ward areas, nurses’ offices, and the MCPPIL office.

Meetings with the clinical consultants and a senior nurse matron were conducted to raise awareness of the study protocol and establish the roles and responsibilities of clinical and research staff.
SECTION 2: RESEARCH MANAGEMENT

2.2.1 ETHICAL APPROVAL AND RESEARCH GOVERNANCE

The research project adhered to the requirements set out in the Department of Health Research Governance Framework. This study received a favourable ethical opinion from the North Wales Research Ethics Committee - West (now renamed as Wales Research Ethics Committee 5). Local research ethics committee approval number = 12/WA/0200.

The study was supported by the Cancer Research UK Liverpool Cancer Trials Unit (LCTU). The LCTU has UKCRC Clinical trials Unit full registration, ensuring high standards of regulatory and quality control. The study was sponsored by the University of Liverpool and adhered to its governance framework. The University of Liverpool was responsible for the authorisations and approvals associated with the research and the professional indemnity and clinical trials insurance applied as appropriate.

The participant information sheet(s) stated that all information will be treated as confidential. The General Practitioner (GP) of the participant was contacted, in writing, to inform them of the involvement of their patient in the research study (appendix 5).

The study was included in the LCTU portfolio. Individuals from the LCTU provided expert advice for aspects of the study. This included a statistician to provide guidance with the sample size calculation and statistical analysis; methodological support was provided from the research scientists. Monthly updates were made to the LCTU management board to provide details of the study progress. The senior hospice management team (consisting of the hospice manager and senior healthcare professionals) provided the research team with the necessary approval to allow the study to take place in the hospice.

The research protocol was modified appropriately in light of external peer-review that was received from the joint scientific committee of Marie Curie Cancer Care and Cancer Research UK.
2.2.2 PROJECT MANAGEMENT GROUP

A project management structure was created to provide direction and support for the research. This included a Project Management Group (PMG) to monitor and advise the progress of the research study. The group included individuals with relevant knowledge for the project, including care of the dying, research methods and data analysis. Specifically, the group included a professor in physiology, a professor in palliative care and a senior clinical-academic in palliative care. The group provided relevant specialist advice and support (clinical and research) at all stages of the project and met quarterly during the project.

Relevant stakeholders were involved from study design through to completion. This included a service-user representative from the Merseyside and Cheshire Cancer Network who provided a lay perspective to the research study. A senior biochemist provided advice about the appropriate biochemical tests, method of collection, analysis and reference ranges.

2.2.3 FUNDING

The researcher’s salary was supported by funds from the MCPCIL and the Institute of Translational Medicine, University of Liverpool. Equipment and laboratory costs were funded by a £10,000 grant from the Friends of the University of Liverpool.

2.2.4 COPYRIGHT AND INTELLECTUAL PROPERTY

Prior to use and reproduction of the Dehydration Symptom Questionnaire (Burge 1991\textsuperscript{269}) and the Dehydration Score (Morita 2006\textsuperscript{228}) permission was obtained from the authors and publisher possessing copyright to the material.\textsuperscript{270,271}
SECTION 3: EXPERIMENTAL DESIGN

2.3.1 PILOT NATURE OF THE STUDY

This study was designed to be pilot in nature. Pilot studies are smaller versions of the main study that are run to test whether the components of the future main study can all work together. They are focused on the processes of the main study, for example to ensure recruitment, randomisation, treatment, and follow-up assessments all run smoothly.\(^{272,273}\)

It is envisaged that this study will lead to a future study, using similar methodology, to facilitate in-depth analysis of BIA with a larger sample size sub-analysed by age, gender, cancer diagnosis, body mass index (BMI) and performance status. Specifically, this study was designed to use BIA and BIVA to evaluate hydration states and determine its relationship with biochemical investigations, clinical examination and self-reported symptoms in advanced cancer. Furthermore, analysis of survival (using several variables) and the follow-up assessments were conducted to obtain information about survival patterns and the practicality, tolerability of repeat assessments.

2.3.2 RECRUITMENT PROCESS

A co-ordinated recruitment schedule was established for participants meeting the eligibility criteria (appendix 6). The research protocol was carefully designed to minimise any coercion. Potential participants were initially approached by a member of the clinical team, who discussed the research study with eligible subjects and were asked if they were happy to discuss the study with a researcher. Individuals expressing interest in the research were met by the researcher who explained the study in greater depth. All patients were provided with a participant information sheet (appendix 7) which provided a brief overview of the study. Following the initial meeting with the patient, the researcher returned 24 hours later to discuss questions or concerns and to determine whether the individual would like to participate in the study. Consequently, all individuals were provided with a minimum of 24 hours to decide on whether they were happy to participate.
Potential participants were informed that their clinical care would not be influenced by their decision to agree or decline participation in the study. Whilst discussing and undertaking the study, procedures to ensure confidentiality and privacy for, and reduce the possibility of influence on other patients were taken (e.g. using interview rooms where possible and ensuring privacy during assessments). Those expressing interest in participating were provided with more detailed study information (appendix 8) and a further opportunity to discuss with the researcher before proceeding to provide formal consent.

The researcher had no day-to-day clinical responsibility for the research participants. The researcher was responsible for providing clinical cover to patients attending the community day-care centre and was part of an emergency out-of-hours on-call rota for hospice inpatients. However, no research activity took place during these occasions and the research ethics committee were satisfied there was no conflict of interest.

2.3.3 CONSENT PROCESS

Fully informed consent was obtained from those willing to participate. Individuals agreeing to participate were screened to ensure eligibility for study entry (appendix 9). Only those fulfilling the requirements for study entry were included. The researcher assessed the patients to ensure that they understood the research study, including the potential risks and benefits. Eligible patients were then asked to sign the consent form in the presence of the researcher (appendix 10). The original consent form was filed in the clinical case notes and copies were given to the patient and filed in the researcher file. A letter was written to patients’ general practitioner (GP) to inform them of their inclusion in the study.

2.3.4 RATIONALE FOR BLOOD TEST PROTOCOL

In order to be eligible for participation participants were required to have biochemical tests (serum urea and creatinine) taken within the previous 72 hours as part of their clinical care. The research team did not ask the clinical team to conduct blood tests for the purposes of the study.
The decision to only include individuals receiving blood investigations in the previous 72 hours was made to maintain the observational nature of the study and to avoid subjecting the participant to additional tests, which may be burdensome. Patients who wished to participate in the study who did not have blood tests performed in the previous 72 hours were eligible to enrol if/when the appropriate blood tests were taken by the clinical team. As the majority of inpatient admissions to the hospice receive a blood test at some point of their admission (usually for monitoring purposes) it was envisaged that most patients would have the opportunity to participate, provided that they satisfied the other eligibility criteria. Blood biochemistry is generally not performed in situations where they are deemed to offer little benefit (for example in the dying phase), and pending discharge.

The 72-hour time interval was chosen to provide the opportunity for participation to as many patients as possible. Ideally, it may be argued that recruitment should occur on the same day the biochemical tests were taken (in order to effectively compare the study assessment methods). However, it was thought that this timeframe may have caused the exclusion of many participants.

2.3.5 ASSESSMENT SCHEDULE

All assessments were conducted in the morning, at a time convenient to the participant, between 9am – 12pm. A co-ordinated protocol for the study assessments was used for the research assessments in the study (appendix 11). Following this, participants were eligible to receive repeat ‘follow-on’ assessments if further biochemical blood tests were investigations repeated by the clinical team (see section 2.3.5.2).

2.3.5.1 BASELINE ASSESSMENT

All participants in the study received the following assessments below performed in this order:

1. Demographic details
2. Clinical assessment
3. Hydration questionnaire
4. Height and weight assessment
5. Bioelectrical impedance assessments
6. Fluid intake review
7. Medication review
8. Urine collection

2.3.5.2 SUBSEQUENT ASSESSMENTS

Patients were eligible for repeat assessments on each subsequent occasion that serum biochemistry investigations (serum urea and creatinine recorded in previous 72 hours) were performed by the clinical team (appendix 11). Eligible patients were identified on a daily basis through discussion with the clinical team, case-note review and review of the electronic blood result system. Subsequent assessments only took place if the participant provided assent on each occasion. Participants who were discharged and later re-admitted were eligible to receive ‘follow-on’ assessments provided that they still met the eligibility criteria. No further assessments were conducted if the participant declined or was unable to provide assent (for example, if unconscious). In these situations, the researcher would liaise with clinical team to determine their opinion of the appropriateness of the patients continued participation in the study. If the clinical team felt that participation was still possible, the researcher would re-approach the participant when they were more conscious. If the clinical team felt that research was currently inappropriate the researcher made no further approach, unless the condition of the participant improved to the level that they were able to re-engage in a discussion about the study.

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\(^{i}\) Weight was not recorded if the patient was physically unable to stand.

\(^{ii}\) Urine was not recorded if the patient was unable to provide a sample.
Repeat assessments for these patients included: bioelectrical impedance measurement, hydration questionnaire, fluid intake assessment, clinical assessment of hydration, medication review, biochemical investigations. No further measurements were collected from participants unable to consent or declining further participation in the study. Information concerning length of inpatient stay, date of discharge, date(s) of repeat admission(s) and of repeat discharge(s). All patients were followed up for 3 months upon the end of the data collection period; date of death was obtained from hospice records. A flow-chart summary of the research project is presented in appendix 12.

2.3.6 MINIMISING HARM

Abnormal blood results, of clinical significance, arising from the study (for example, hypercalcaemia detected through an add-on test of an existing serum biochemistry sample) were passed on to the clinical team. The researcher was not involved in any clinical decision making. In order to guide appropriate care, the researcher informed the clinical team about patients visibly scoring >50mm on the visual analogue scale for the first six symptoms (thirst, pain, dry mouth, nausea, unpleasant taste and fatigue) and <50mm for the final symptom (pleasure in drinking) of the Burge Dehydration Symptom Questionnaire. The document used for data collection is available in appendix 13.
SECTION 4: STUDY MEASUREMENT AND TOOLS

2.4.1 DEMOGRAPHIC DETAILS

The following information was obtained from the medical case notes: age (years), gender (male/female) and ethnicity. Ethnicity data was recorded according to the format defined by the National Ethnic Code classification as listed in Health and Social Care Information Centre (see Table 3).274

TABLE 3: NATIONAL ETHNICITY CODE DATA (AS DEFINED BY THE HEALTH AND SOCIAL CARE INFORMATION CENTRE274)

<table>
<thead>
<tr>
<th>White</th>
<th>Mixed</th>
<th>Black or Black British</th>
<th>Asian or Asian British</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>British</td>
<td>White and black</td>
<td>Caribbean</td>
<td>Indian</td>
<td>Chinese</td>
</tr>
<tr>
<td>Irish</td>
<td>Caribbean</td>
<td>Caribbean</td>
<td>Pakistani</td>
<td>Any other ethnic group</td>
</tr>
<tr>
<td>Any other mixed background</td>
<td>White and Black African</td>
<td>Any other Black background</td>
<td>Bangladeshi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White and Asian</td>
<td>Any other mixed</td>
<td>Any other Asian</td>
<td>background</td>
</tr>
<tr>
<td></td>
<td>background</td>
<td>background</td>
<td>background</td>
<td></td>
</tr>
</tbody>
</table>

Details of the cancer diagnosis were recorded according to the subtypes as defined by the International Classification of Diseases.267 Information recorded included: the primary site of cancer, presence of metastases (yes/no), location of metastases and disease co-morbidities (appendix 14). Date of admission and date of BIA assessment were recorded.
2.4.2 MEDICATION REVIEW

All prescribed medications (name, dose and route) were recorded. The presence of serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitor (SNRI) and diuretics were recorded (yes/no). These medications were identified from lists provided in the British National Formulary (Table 4).

**TABLE 4: LIST OF SSRI, SNRI AND DIURETIC MEDICATIONS AS LISTED IN THE BRITISH NATIONAL FORMULARY (BNF)**

<table>
<thead>
<tr>
<th>SSRI</th>
<th>SNRI</th>
<th>Diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>Duloxetine</td>
<td>Thiazides (bendroflumethiazide, chlortalidone, cyclopenthiazide, indapamide, metolazone, xipamide)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Venlafaxine</td>
<td>Loop diuretics (furosemide, bumetanide, torasemide)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td>Potassium-sparing diuretics (amiloride, triamterene)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td>Potassium-sparing with other diuretics (co-amilozide, navispare, co-amilofruse, co-triamterzide)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td>Aldosterone antagonists (eplerenone, spironolactone)</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
<td>Osmotic diuretics (mannitol)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbonic anhydrase inhibitors (acetazolamide)</td>
</tr>
</tbody>
</table>

The Anticholinergic Burden (ACB) scale (appendix 15) was used to calculate the burden of anticholinergic drugs. Here, medications receive a score in light of their reported anticholinergic effects (1 = mild, 2 = moderate; 3 = severe). A total ACB score was calculated for each patient through addition of the ACB score from each medication taken. A total ACB score of three or more is considered clinically significant.
Total daily opioid dose, at the time of assessment, was calculated. This included regular by the clock opioids by oral, subcutaneous and transdermal routes. As required (PRN) medications were not included in this total. Opioid equivalency is highly disputed with notable variations in the opioid conversions utilised in clinical practice. Consequently, the Palliative Care Formulary and a recent systematic review about opioid conversions were evaluated to determine acceptable opioid conversions which could be used for the purposes of opioid conversions in this study. Although these references provide recent evidence of opioid equi-analgesia, it is acknowledging that there are variations in accepted practice (Table 5).

**TABLE 5: CONVERSION RATIOS FOR OPIOIDS (DEVELOPED FROM MERCADANTE ET AL 2011 AND TWYCROSS ET AL 2011)**

<table>
<thead>
<tr>
<th>NAME</th>
<th>Equivalence compared to oral morphine</th>
<th>Calculation required compared to oral morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO Morphine</td>
<td>1:1</td>
<td>Same dose</td>
</tr>
<tr>
<td>SC Morphine</td>
<td>2:1</td>
<td>Multiply by 2</td>
</tr>
<tr>
<td>PO Oxycodone</td>
<td>1.5:1</td>
<td>Multiply by 1.5</td>
</tr>
<tr>
<td>SC Oxycodone</td>
<td>2:1</td>
<td>Multiply by 2</td>
</tr>
<tr>
<td>SC Diamorphine</td>
<td>3:1</td>
<td>Multiply by 3</td>
</tr>
<tr>
<td>PO Hydromorphone</td>
<td>5:1</td>
<td>Multiply by 5</td>
</tr>
<tr>
<td>SC Hydromorphone</td>
<td>10:1</td>
<td>Multiply by 10</td>
</tr>
<tr>
<td>SC Alfentanil</td>
<td>30:1</td>
<td>Multiply by 30</td>
</tr>
<tr>
<td>TD Fentanyl (micrograms per hour)</td>
<td>100:1</td>
<td>Multiply fentanyl ug/hr dose by 24 for total daily dose (mg)</td>
</tr>
<tr>
<td>TD Buprenorphine</td>
<td>100:1</td>
<td>Multiply fentanyl ug/hr dose by 24 for total daily dose (mg)</td>
</tr>
<tr>
<td>PO Dihydrocodeine</td>
<td>1:5</td>
<td>Divide by 5</td>
</tr>
<tr>
<td>PO Codeine</td>
<td>1:10</td>
<td>Divide by 10</td>
</tr>
<tr>
<td>PO Tramadol</td>
<td>1:10</td>
<td>Divide by 10</td>
</tr>
</tbody>
</table>
2.4.3 CLINICAL ASSESSMENT

Performance status was recorded using the Eastern Cooperative Oncology Group (ECOG) scale.\textsuperscript{282} ECOG performance status scale is a validated scale to record performance status using a six point scale (0 = fully active, 5 = dead).

**TABLE 6: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE\textsuperscript{282}**

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

The presence of audible secretions from the edge of the bed was recorded (yes/no). The presence of oedema (defined as the presence of superficial swelling on the face, trunk, abdomen or the upper or lower extremities) was also recorded (yes/no).

2.4.4 DEHYDRATION SYMPTOM QUESTIONNAIRE – BURGE ET AL \textsuperscript{1991}\textsuperscript{250} \textsuperscript{269}

Participants completed a brief hydration symptom questionnaire developed by Burge.\textsuperscript{269} This comprises of seven questions asking participants to rate the severity of their symptoms in the last 24-hours using a 100mm Visual Analogue Scale (VAS). The VAS is a simple visual rating scale which allows patients to rate symptom intensity. The seven symptoms included were thirst, pain, dry mouth, nausea, taste, fatigue and pleasure from drinking (appendix 16). In situations where the participant was unable to complete the questionnaire (for, example due to
weakness), the individual was asked to point to an approximate point on the line which was then marked by the researcher.

The dehydration symptom questionnaire was developed based on the existing evidence that demonstrates self-reports of symptom distress are reliable and valid. Previous non-cancer studies have examined thirst and dry mouth VAS scores in dehydration. In these studies, test-retest reliability for the thirst and dry mouth VAS was good, reported at 0.79 (p<0.001) for week to week observations over two months for haemodialysis patients.

The Burge Dehydration Symptom Questionnaire features seven items (pain, dry mouth, thirst, unpleasant taste, fatigue and pleasure in drinking). The variables nausea, pain and fatigue were adapted from the Symptom Distress Scale, a thirteen item Likert self-report tool used in patients with chronic illness and cancer (internal consistency coefficient alpha 0.79-0.89). The oral symptom variables were incorporated on account of evidence reported in non-cancer studies. The overall reliability for the full questionnaire has a Cronbach’s alpha value of 0.62, which is below the ≥0.7 level commonly quoted as necessary to ensure reliability for research studies. However, when thirst, dry mouth, bad taste and fatigue were combined the reported alpha increased to 0.72. Cronbach's alpha is a measure of internal consistency (how closely related a set of items are as a group), a measure of the scale reliability. The validity of the assessment tool has not been examined outside of the original Burge thesis. The Burge Dehydration Questionnaire was chosen for this study as it is the only dehydration symptom questionnaire developed for use (and tested) in advanced cancer patients. The alpha value of 0.72 for thirst, dry mouth, bad taste and fatigue provides evidence of its reliability for use for this purpose and population. Additionally, the short testing time and ease of administration was suited to the target population.

2.4.5 DEHYDRATION ASSESSMENT SCALE – MORITA ET AL 2005

A dehydration score was calculated using the approach taken by Morita et al, based on a simple total of scores from three physical findings: moisture on the mucous membranes of the mouth (0: moist, 1: somewhat dry, 2: dry), axillary
moisture (0: moist, 1: dry), and sunkenness of eyes (0: normal, 1: slightly sunken, 2: sunken) (appendix 17). These signs were selected by the author on the basis of their significant correlations with biological dehydration, as previously confirmed in elderly patients. \textsuperscript{225 226 231 250} Empirical studies have found that the sensitivity/specificity of each sign in identifying dehydration is 85%/58%, 50%/82%, and 62%/82%, respectively. \textsuperscript{225 226 231} A total hydration status score was calculated from the sum of these scores (range 0-5) with higher scores indicating an increased chance of dehydration. A cut-off of ≥2 is predictive of biochemical dehydration and has been used by other authors to study hydration in advanced cancer patients. \textsuperscript{230 292} Although the Morita Dehydration Assessment Scale has been used by various authors for the evaluation of fluid states, the reliability and validity of this tool has not been established in the literature. However, the tool was used in this study as it represented the best (and only) available clinical assessment tool evaluation of hydration-related physical signs in advanced cancer.

2.4.6 ORAL INTAKE FLUID ASSESSMENT

Fluid intake was documented for all patients based on standard nursing documentation. Patients routinely had fluid intake recorded on admission by nursing staff in reference to the patients’ fluid intake and oral health. Assessments were repeated on a weekly basis but were conducted in greater frequency in those with poor oral intake (appendix 18). \textsuperscript{293} The most recent assessment of fluid intake was documented. Oral fluid intake was classified into one of the following categories accordingly the fluid intake for the preceding 24 hours: 0 - 199ml, 200-499ml, 500-799 or >800mls.

2.4.7 HEIGHT AND WEIGHT ASSESSMENT

Height (H) was measured, without shoes, to the nearest 0.1 cm using a portable stadiometer (SECA© 213 Height Measure / Stadiometer). Due to debility, some patients were unable to stand; in these instances their length was measured horizontally with the patient lying in the bed. The stadiometer was chosen as it
lightweight and collapsible, enabling horizontal assessments in the situations where participants were unable to stand.

Body weight (W) was measured, in the morning to the nearest 0.1kg (SECA© 955 High Capacity Electronic Chair Scale). Weight was not assessed in circumstances where the patient was unable to transfer safely to the weighing scale. Weight and height were used to calculate body mass index \( W/[kg]/H^2/[m] \).

### 2.4.8 BIOCHEMICAL INVESTIGATIONS

The following biochemistry blood results were recorded if performed on admission:

Urea (mmol/l), creatinine (\( \mu \)mol/l), serum sodium (mmol/l), serum albumin (g/L), adjusted calcium (mmol/l). Where possible, a urine sample was obtained from participant to obtain the urine osmolality (mosm/kg). The researcher contacted the laboratory to request the addition of the serum osmolality (mosm/kg) test to the current serum sample for all patients.

Participants were defined as having pre-renal failure if the serum urea:creatinine ratio \( \geq 100 \) (mmol/mmol). For example, a patient with a urea of 33.8 mmol/l and creatinine of 176 \( \mu \)mol/l would have a urea:creatinine ratio of 192.05 mmol:mmol.

The \( \geq 100 \) cut-off is indicative of pre-renal failure which is often caused by hypovolaemia. This biochemical definition was chosen based on the similar work in previous studies and on the basis of expert recommendations from a clinical biochemist and a physiologist.

### 2.4.9 BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

The EFG\(^3\) ElectroFluidGraph Vector Impedance Analyser (Akern©) was used for the bio-impedance assessments. The method involved a tetra-polar technique to deliver a single frequency current of 50kHz (\( \pm 5\% \)) to each participant. The external calibration of the analyser was checked with a calibration circuit of known impedance value \( r = 470 \Omega, Xc = 90\Omega \) in the morning of each testing session. All patients were assessed between 9am – 12pm. The BIA testing procedure (appendix

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\(^{iii}\) In the UK creatinine is often reported as micromol. Therefore this value was divided by 1000.
was conducted in line with methods described by Lukaski and the BIA recommendations described elsewhere. The participants were lightly clothed, lying in the supine horizontal position on the bed, without shoes or socks. Their arms were positioned 30 degrees from the body with the legs positioned 45 degrees away from each other. Two disposable pre-gelled aluminium electrodes (Akern©) were affixed to the dorsum of the right hand (one placed on the edge of an imaginary line bisecting the ulnar head and the other on the middle finger proximal to the metacarpal-phalangeal) and two to the dorsum of the right foot (one placed medially, to an imaginary line bisecting the medical malleolus at the ankle and the other proximal to the metatarsal-phalangeal joints) (Figure 12). The current-introducing electrodes are placed a minimum distance of the diameter of the wrist or ankle of the paired electrode.

BIVA was chosen as the primary assessment tool as it provided a method to: (i) classify static hydration states of individuals according to the position of individual vectors on the RXc graph; (ii) to compare hydration between groups of patients according to various classifications (e.g. oedematous vs. not-oedematous); (iii) to evaluate change in fluid status over time through longitudinal assessments; and (iv) to compare hydration status for the sample with other cancer populations from the literature. The \( H^2/R \) was also used in this study to measure hydration (due its high correlation of \( H^2/R \) with TBW) between individuals. Compared to \( H^2/R \), the BIVA method provides more useful information about hydration as it involves the measurement of both resistance and reactance (as opposed to \( H^2/R \) which only involves assessment of R).

BIVA and \( H^2/R \) were used for the main statistical analysis in this study in favour of individual raw BIA measurements (i.e. R, Xc and PA). Concerning hydration, more information is obtained through the interpretation of R and Xc as part of the BIVA method or the incorporation of R into the \( H^2/R \) equation. PA was not studied in this analysis; although useful prognostic indicator its association with hydration has not been established. Therefore it was not felt that the inclusion of PA would improve the data analysis.
FIGURE 12: DIAGRAM SHOWING ELECTRODE PLACEMENT REQUIRED FOR THE BIA TEST

2.4.9.1 CHOICE OF THE REFERENCE POPULATION

BIVA requires standardisation to an appropriate reference population. For this study a non-cancer population was chosen as the reference. This reference comprises of an Italian hospital inpatient population of males (n=354) and females (n=372) Caucasian patients aged between 18-85 without cancer (Table 7). The population was chosen as it was the most similar in characteristics (age, ethnicity and body mass) to this sample.

TABLE 7: DETAILS OF THE REFERENCE POPULATION OF PICCOLI 1995

<table>
<thead>
<tr>
<th>Popn. Size, N</th>
<th>R/H Mean</th>
<th>R/H SD</th>
<th>Xc/H Mean</th>
<th>Xc/H SD</th>
<th>Correlation r (R/H, Xc/H)</th>
<th>Sex (M/F)</th>
<th>BMI</th>
<th>Analyser</th>
</tr>
</thead>
<tbody>
<tr>
<td>354</td>
<td>298.6</td>
<td>43.2</td>
<td>30.8</td>
<td>7.2</td>
<td>0.47</td>
<td>m</td>
<td>16-31</td>
<td>Akern-RJL Systems</td>
</tr>
<tr>
<td>372</td>
<td>371.9</td>
<td>49.0</td>
<td>34.4</td>
<td>7.7</td>
<td>0.41</td>
<td>f</td>
<td>16-31</td>
<td>Akern-RJL Systems</td>
</tr>
</tbody>
</table>
SECTION 5: STATISTICAL ANALYSIS OF DATA

2.5.1 STATISTICAL ANALYSIS PLAN

The statistical analysis began with a descriptive analysis of the data (chapter 3). Initially, each target variable was assessed for normality using the Shapiro-Wilk test. Parametric and non-parametric tests were used as appropriate. Statistical Package for the Social Sciences (SPSS) version 21.0 was used for standard calculations. Frequency analysis with the chi-squared test, Student t test, the Mann-Whitney U test, as appropriate, to compare differences between groups and variables. For the independent t-tests, Levene’s test for homogeneity of variance was used to examine the quality of variances within a population to identify whether derivatives required exclusion or separate analysis from the cohort. The linear correlation coefficient \( r \), Pearson’s correlation coefficient and Spearman’s rank correlation coefficient were appropriately used to evaluate correlations between variables. Multiple linear regression was used to evaluate associations of variables.

BIA vector analysis was conducted using a Microsoft Excel programme developed by Professor Antonio Piccoli, University of Padova. Hotelling’s \( T^2 \) test for vector analysis was used to compare for significant difference between mean vector distances (D). Survival was evaluated from the date of first BIA measurement to the date of death using log-rank Kaplan-Meier survival and hazard ratios, according to categorical bio-impedance and biochemical indices.

The following methods were conducted to achieve the study objectives.

2.5.1.1 OBJECTIVE 1

Dehydration symptom scores were evaluated using box plot analysis of the participant reported scores obtained from the Burge symptom questionnaire. This data was compared to the original Burge study, in order, to determine the level of agreement between the two study populations. The impedance index \( (H^2/R) \) was calculated from the BIA raw variables to provide a proxy measurement of total body water.
Multiple regression analysis was conducted to further study the relationship between several predictor variables with $H^2/R$, in order, to evaluate potential relationships of TBW with patient demographics (age, gender), clinical measurements (Morita dehydration score, oedema presence) serum biochemistry (ur:cr) and self-reported symptoms (Burge-4 score). A separate regression analysis was performed to evaluate whether the Burge-4 score was associated with concurrent use of medications known to cause symptoms (dry mouth, thirst, unpleasant taste and fatigue). This analysis included the ACB score, total daily morphine dose, presence of diuretic medication and use of SNRI and/or SSRI medications.

### 2.5.1.2 OBJECTIVE 2

BIVA was conducted to evaluate hydration in the sample. The RXc point graph was used to assess participant’s hydration status according to tolerance ellipses from a non-cancer reference population. Data were plotted on the graph with the 50%, 75% and 95% tolerance intervals.

Hydration status was determined by the individual’s baseline bio-impedance vector position on the BIVA RXc normogram. The graph was divided into five parallel sections on the hydration axis (Figure 6). Individuals with vectors falling in (or above) the 76th percentile upper range were severely less-hydrated (point 1) and those with vectors in the 51–75% upper range were mildly less-hydrated (point 2). Participants with vectors in the central 50th percentile ellipse were normally-hydrated (point 3). Those with vectors in the lower 51 – 75% percentile range were mildly more-hydrated (point 4) whereas vectors in (or below) the lower 76th percentile range were severely more-hydrated (point 5). Based on the above criteria, hydration states were summarised into three categories, consisting of less-hydration (severe and mild), normal hydration and more-hydration (severe and mild). Further simplification grouped participants as either less-hydrated (mild and severe) or not less-hydrated (normally-hydrated and more-hydrated patients).

Less-hydrated and not less-hydrated patients were compared to assess for differences in biochemistry, self-reported symptoms (Burge questionnaire), clinical
signs (Morita dehydration questionnaire), oral fluid intake and performance status (ECOG). Student’s t-test was used to compare continuous variables and Mann U Whitney was used to evaluate ordinal data.

BIVA mean vectors were plotted with their 95% confidence ellipses. Mean vectors were used to compare for differences between groups based on the following variables and associated cut-offs: oedema present (yes/no), Burge-4 score (mean), Morita dehydration score (< or ≥2
dow), secretions present (yes/no), ECOG (< or ≥ cut-off values of 2, 3 and 4) and whether pre-renal failure was present (yes/no).

Burge-4 sub-items (thirst, dry mouth, unpleasant taste and fatigue) were further analysed, using cut-off VAS scores of < or ≥50mm. The two-sample Hotelling’s T² test was used to compare differences in the mean vectors between groups.150

The mean R/H and Xc/H values for male and females were converted to Z-scores and plotted on the RXc Z-score graph. The R/H and Xc/H values for seven other cancer populations (lung cancer,98 158 breast cancer,297 head and neck cancer206 298) were obtained from the literature and converted to the Z-score graph in respect to their reference populations (Figure 10). The Z-score obtained from this population was compared from the data from these previous studies using the RXc Z-score graph method.144

2.5.1.3 OBJECTIVE 3

Survival was analysed using Kaplan-Meier log-rank test and Cox regression analysis. All patients were followed up for 3 months following the end of the study data collection. Survival time was recorded in days from the first data of assessment to the date of death (if applicable). Kaplan-Meier analysis was used to analyse survival according to hydration classification and the presence or absence of pre-renal failure. Cox regression analysis was used to obtain hazard ratios for death for ur:cr

---

ratio and $H^2/R$. Hydration classification (according to BIVA), $H^2/R$ and $ur:cr$ ratio were combined in a regression equation with other factors (age, gender, ECOG and the presence of metastatic disease) to evaluate the potential confounding influence of associated variables.

2.5.1.4 OBJECTIVE 4

The frequency of assessments was described for participants receiving multiple assessments. The overall change of vector position from the first and last assessments was evaluated by calculation of the difference of resistance ($dR/H$) and reactance $dXc/H$. The mean difference, standard deviation and r correlation of $dR/H$ and $dXc/H$ was plotted on the $RXc$ paired graph with the associated 95% tolerance ellipse. Paired vector data was statically analysed using the paired Hotelling’s $T^2$ test. The difference in $H^2/R$, and the $ur:cr$ ratio was calculated for those receiving multiple assessments. Kaplan-Meier survival analysis was conducted to determine whether participants experiencing change in $H^2/R$ or $ur:cr$ ratio affected survival. For this analysis, an increase in the $H^2/R$ (suggesting less TBW) was evaluated against no change or a decrease (suggesting static or more-hydrated states). Similarly, an increase in $ur:cr$ ratio (suggesting worsening renal function) was evaluated against no change or a decrease (suggesting static or improving renal function).

2.5.2 OUTCOME / DEPENDENT VARIABLES

The dependent (outcome) variables consisted of the $H^2/R$ and the bio-impedance measures standardised by height ($R/H$ and $Xc/H$) as part of a vector analysis of the BIA data.

2.5.3 PREDICTORS / INDEPENDENT VARIABLES

The independent variables were the summated score for four variables of the Burge Dehydration Questionnaire (thirst, dry mouth, unpleasant taste and fatigue); the individual Burge questionnaire symptom scores; the Morita Dehydration Score, presence (or absence) of oedema, ECOG performance status, and the $ur:cr$ ratio.
2.5.4 SAMPLE SIZE CALCULATION

A prospective sample size calculation was difficult in light of the absence of similar studies comparing the relationships between BIA, body composition, symptoms, and clinical examination and biochemical measures in palliative patients. In view of the lack of information available for potential recruitment rates, an exploratory sample size 90 patients was calculated, based on admissions data from the Marie Curie Hospice Liverpool.267

To draw a vector for the palliative population on the RXc graph to enable comparisons with other reference populations: A sample size of 90 will give a 95% confidence region for the mean vector of the vector random variable \((Z(R), Z(Xc))\) as an ellipse with semi-axes of approximate lengths of 0.33 and 0.16. For the two-group analysis, a sample size of 45 for each of two groups will have power of 0.8 for detecting a difference of \((0.5, 0.5)\) in the mean BIVA vectors either group, for significance level of 0.05.
CHAPTER 3: THE USE OF BIA TO EVALUATE HYDRATION AND INVESTIGATE ITS RELATIONSHIP WITH BIOCHEMICAL INVESTIGATION, CLINICAL EXAMINATION AND SELF-REPORTED SYMPTOMS IN ADVANCED CANCER

SECTION 1: RECRUITMENT AND DEMOGRAPHIC DETAILS

3.1.1 INTRODUCTION

Within this section the demographics of the study participants are presented. This includes a description of the patient characteristics, which involves details about serum biochemistry, symptomatic burden, medication use, oral fluid intake and the bio-impedance measurements. Following this, section 2 presents the results of the multiple regression analysis which was conducted to evaluate how hydration (as measured by the $H^2/R$) relates to clinical measurements, biochemistry and self-reported symptoms.

3.1.2 RECRUITMENT (FIGURE 13)

Patients were recruited between the period of December 2012 and October 2013. A total of 118 patients were identified as eligible to enter the study and were initially approached by the clinical team. The study successfully achieved the indicative recruitment target of 90 patients with a recruitment rate of 76.3%.
FIGURE 13: RECRUITMENT RESULTS FLOWCHART

Patients identified by clinical team (n=118)

Patients approached by researcher (n= 115)

Eligible participants identified by researcher (n=113)

Patients providing informed consent (n= 90)

Patients declining invitation to speak to researcher (n=3)

Ineligible (n=2)
- Pacemaker (n=1)
- Unable to comply with assessments (n=1)

Exclusions (n= 23)
- Patient declined (n=11)
- Too unwell to participate (n=10)
- Discharged before assessment took place (n=2)
3.1.3 PATIENT DEMOGRAPHICS (TABLE 8)

Overall, there was a fairly equal gender split of participants with 42 (46.7%) males and 48 (53.3%) females. The mean age of participants was 71.2 with majority of Caucasian ethnicity patients (n=89, 98.9%). Nineteen different types of cancers were recorded with lung cancer the most common (n=14, 15.6%). Most participants had an ECOG performance status of 3 (n=36, 40%); no patients had a performance status of ECOG-0. Weight was measured in 28 patients (it was not possible to weigh the remaining patients due to physical debility). For these patients, mean weight was 69.45kg (SD=17.90), mean body mass index (BMI) for the sample was 25.17 kg/m$^2$ (SD=4.98). Oedema was present in a third of the sample (n=27, 30%). The mean results of the BIA raw variables of the study population are presented in table 9. These mean values provide the BIA population data for this sample which will be useful for comparisons, using BIVA, with this dataset.

**TABLE 8: DEMOGRAPHIC DETAILS OF STUDY PARTICIPANTS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (± SD), years</td>
<td>71.17 (12.21)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>46.7</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>53.3</td>
</tr>
<tr>
<td>Mean height (± SD), cm</td>
<td>164.22 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Mean weight (± SD), kg</td>
<td>69.45 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Mean body mass index (± SD), kg/m$^2$</td>
<td>25.17 (4.98)</td>
<td></td>
</tr>
</tbody>
</table>

*Race/ethnicity*

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>89</td>
<td>98.9</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*ECOG*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Characteristic</td>
<td>N</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Oedema present</td>
<td>27</td>
</tr>
<tr>
<td>Metastatic disease present</td>
<td>64</td>
</tr>
</tbody>
</table>

*Cancer diagnosis*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>14</td>
<td>15.6</td>
</tr>
<tr>
<td>Colorectal</td>
<td>11</td>
<td>12.2</td>
</tr>
<tr>
<td>Prostate</td>
<td>10</td>
<td>11.1</td>
</tr>
<tr>
<td>Ovarian</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>Breast</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>Myeloma</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>Cervical</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Gastric</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Brain</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Soft tissue/muscle/connective tissue</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Groin</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Uterus</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Tongue</td>
<td>1</td>
<td>1.1</td>
</tr>
</tbody>
</table>
### TABLE 9: MEAN BASELINE BIO-IMPEDANCE SCORES FOR THE SAMPLE (N=90)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RH</td>
<td>341.58</td>
<td>82.22</td>
</tr>
<tr>
<td>XcH</td>
<td>27.68</td>
<td>9.49</td>
</tr>
<tr>
<td>PA</td>
<td>4.71</td>
<td>1.33</td>
</tr>
<tr>
<td>$H^2/R$</td>
<td>51.58</td>
<td>15.41</td>
</tr>
</tbody>
</table>

### 3.1.4 STUDY OBSERVATIONS (TABLE 10)

A total of 126 study assessments were undertaken. Twenty-four (26.7%) participants received multiple assessments. Twenty-two patients (24.4%) were able to provide urine for analysis (the remainder were unable to provide a sample during the collection period or were without a catheter and were unable to mobilise).

### TABLE 10: THE NUMBER OF STUDY ASSESSMENTS

<table>
<thead>
<tr>
<th>Number of study assessments</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>73.3</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>16.7</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>7.8</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number or urine assessments</th>
<th>N</th>
<th>% of 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>24.4</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>31.1</td>
</tr>
</tbody>
</table>

### 3.1.5 MORITA DEHYDRATION SCORE (TABLE 11)

The majority of sample had a Morita dehydration score of either one (n=25, 27.8%), two (n=23, 25.6%) or three (n=20, 22.2%) respectively.
### TABLE 11: MORITA DEHYDRATION SCORE RESULTS FOR THE SAMPLE

<table>
<thead>
<tr>
<th>Morita dehydration score</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13</td>
<td>14.4</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>27.8</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>25.6</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>22.2</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>7.8</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

#### 3.1.6 ORAL FLUID INTAKE (TABLE 12)

Most patients had a daily oral fluid intake of 500 - 799mls per day (n=42, 46.7%) whereas a lower fluid intake of 0-199mls/day was observed least frequently (n=4, 4.4%). As few numbers of participants had an oral intake of less than 200mls, the 0-199mls category was grouped together with the 200-499mls group to simplify the data analysis. The resultant category demonstrated how 27 (30%) patients had an oral intake of 0-499mls.

### TABLE 12: ORAL FLUID INTAKE INFORMATION

<table>
<thead>
<tr>
<th>Oral intake (mls)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-199</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>200-499</td>
<td>23</td>
<td>25.6</td>
</tr>
<tr>
<td>500 - 799</td>
<td>42</td>
<td>46.7</td>
</tr>
<tr>
<td>≥800</td>
<td>21</td>
<td>23.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified Oral fluid intake (mls)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 499</td>
<td>27</td>
<td>30.0</td>
</tr>
<tr>
<td>500 - 799</td>
<td>42</td>
<td>46.7</td>
</tr>
<tr>
<td>≥800</td>
<td>21</td>
<td>23.3</td>
</tr>
</tbody>
</table>
3.1.7 MEDICATIONS (TABLE 13)

The majority of patients were prescribed opioids (n=65, 72.2%). The mean morphine dose was 60.8mg (SD=86.7) daily. However, this was much higher than the median (24.0mg) which suggests that the mean is higher on account of large doses taken by some of the study participants. Anticholinergic medications were commonly prescribed (n=57, 63.3%) with total Anticholinergic Burden (ACB) scores ranging between 0-7. About a third of all patients had an ACB score of 1 (n=31, 34.4%) whereas 15 (16.7%) had scores ≥3, which suggests severe anticholinergic burden. Both diuretics and SSRI/SNRIs were prescribed in 14 (15.6%) of participants.

TABLE 13: CHARACTERISTICS OF MEDICATIONS TAKEN BY STUDY PARTICIPANTS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids prescribed?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65</td>
<td>72.2</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>17.8</td>
</tr>
<tr>
<td><strong>Mean daily morphine dose (±SD), mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.78 (86.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Median daily morphine dose (IQR), mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.0 (82.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Anticholinergics prescribed?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57</td>
<td>63.3</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>36.7</td>
</tr>
<tr>
<td><strong>Anticholinergic burden score (ACB)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34</td>
<td>37.8</td>
</tr>
<tr>
<td>1</td>
<td>31</td>
<td>34.4</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>11.1</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>8.9</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Characteristic</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Diuretics prescribed?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>15.6</td>
</tr>
<tr>
<td>No</td>
<td>76</td>
<td>84.4</td>
</tr>
<tr>
<td><strong>SSRI and/or SNRI prescribed?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>15.6</td>
</tr>
<tr>
<td>No</td>
<td>76</td>
<td>84.4</td>
</tr>
</tbody>
</table>

### 3.1.8 ANALYSIS OF THE BURGE QUESTIONNAIRE – SYMPTOMS OF DEHYDRATION (TABLE 14; FIGURES 14 & 15)

The Burge questionnaire demonstrates a high prevalence of symptoms at baseline. Overall, fatigue was reported the most severely (M= 63.60, SD =30.09) whereas nausea was less severe (M=25.61, SD=31.26). Pleasure in drinking scored highly (M=68.76 SD=29.08); this suggested that drinking fluids was pleasurable for the majority of patients. Boxplot analysis (Figure 14) provides a visual representation of the results, demonstrating how more than 50% (i.e. median) of patients reported VAS scores of >50mm for the following symptoms: pleasure in drinking (76.0%), fatigue (67.0%), dry mouth (61.5%), thirst (56.5%) and pain (53.5%). Four of the Burge symptom scores (thirst, dry mouth, unpleasant taste and fatigue) were combined to create the Burge-4 dehydration score (Figure 15). The mean Burge-4 score was 222.07 (SD=95.40) was similar to the median and ranged from 4 to 400mm.
TABLE 14: BASELINE DATA FROM THE BURGE DEHYDRATION QUESTIONNAIRE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirst</td>
<td>56.11</td>
<td>29.49</td>
<td>56.50</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Pain</td>
<td>50.09</td>
<td>30.86</td>
<td>53.50</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>60.01</td>
<td>30.64</td>
<td>61.50</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Nausea</td>
<td>25.61</td>
<td>31.26</td>
<td>12.00</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Unpleasant taste</td>
<td>42.34</td>
<td>34.11</td>
<td>42.50</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Fatigue</td>
<td>63.60</td>
<td>30.09</td>
<td>67.00</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Pleasure in drinking</td>
<td>68.76</td>
<td>29.08</td>
<td>76.00</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Burge-4 score (thirst, dry mouth, unpleasant taste and fatigue)</td>
<td>222.07</td>
<td>95.40</td>
<td>220.50</td>
<td>4 - 400</td>
</tr>
</tbody>
</table>

FIGURE 14: REPRESENTATION OF SYMPTOM SCORES FROM THE CURRENT STUDY USING BOX AND WHISKER PLOTS

Data is presented using a box plot and whisker plot. The lower and upper limits of the whiskers correspond to the minimum and maximum values respectively. The lower limit of the box is the 25% quartile, the black bar is the median and the upper limit of the box is the 75% quartile.
FIGURE 15: REPRESENTATION OF THE BURGE-4 SYMPTOM SCORE USING BOX AND WHISKER PLOTS

The lower and upper limits of the whiskers correspond to the minimum and maximum values respectively. The lower limit of the box is the 25% quartile, the black bar is the median and the upper limit of the box is the 75% quartile.

3.1.9 COMPARISON OF SYMPTOM SCORES WITH THE BURGE 1991 DATASET (TABLE 15)

Mean VAS scores were tabulated to compare this dataset to the Burge study 1991. Comparatively, in this study, pain was reported with higher intensity (50.1 vs. 33.5mm). Mean VAS scores for the other variables demonstrated a high level of agreement between the two studies $r(7) = .90$, $p=0.006$. 
TABLE 15: TABLE COMPARING BASELINE MEAN SYMPTOM SCORES FOR THE BURGE 1991 AND NWOSU 2014 STUDIES

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Nwosu 2014</th>
<th>Burge 1991</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirst</td>
<td>56.1</td>
<td>53.8</td>
</tr>
<tr>
<td>Pain</td>
<td>50.1</td>
<td>33.5</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>60.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>25.6</td>
<td>24.0</td>
</tr>
<tr>
<td>Unpleasant taste</td>
<td>42.3</td>
<td>46.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>63.6</td>
<td>61.8</td>
</tr>
<tr>
<td>Pleasure in drinking</td>
<td>68.8</td>
<td>61.6</td>
</tr>
</tbody>
</table>

N 7

Spearman rank correlation (2 tailed) .899
P .006

3.1.10 ANALYSIS OF THE BIOCHEMICAL INVESTIGATIONS (TABLE 16)

The biochemical findings showed that 37 (41.1%) patients had pre-renal failure (i.e. ur:cr >100:1). The mean ur:cr ratio was 96.7 SD=53.16) with a mean eGFR of 72.1 (SD=72.1); this is suggestive of an average eGFR stage of 1 (normal kidney function) or 2 (slightly reduced kidney function).
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
<th>Normal reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/l)</td>
<td>89</td>
<td>136.12</td>
<td>4.28</td>
<td>137</td>
<td>126 - 145</td>
<td>133 - 146</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>90</td>
<td>7.26</td>
<td>4.36</td>
<td>6.9</td>
<td>1.3 – 33.8</td>
<td>2.5 - 7.8</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>90</td>
<td>79.26</td>
<td>30.33</td>
<td>76.5</td>
<td>23 - 183</td>
<td>50 - 130</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>90</td>
<td>72.1</td>
<td>18.77</td>
<td>76.0</td>
<td>24 - 90</td>
<td>0-90</td>
</tr>
<tr>
<td>Ur:cr ratio (mmol/mmol)</td>
<td>90</td>
<td>96.68</td>
<td>53.16</td>
<td>81.16</td>
<td>32.61 –</td>
<td>-</td>
</tr>
<tr>
<td>Ur:cr ratio ≥100 (%)</td>
<td>37</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adjusted calcium (mmol/l)</td>
<td>89</td>
<td>2.32</td>
<td>0.24</td>
<td>2.29</td>
<td>1.65 – 3.5</td>
<td>2.20 -2.60</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>90</td>
<td>32.07</td>
<td>6.08</td>
<td>32</td>
<td>3 - 47</td>
<td>35 - 50</td>
</tr>
<tr>
<td>Serum osmolarity (mosm/kg)</td>
<td>61</td>
<td>286.36</td>
<td>10.03</td>
<td>288</td>
<td>260 - 311</td>
<td>275 - 295</td>
</tr>
<tr>
<td>Urine osmolarity (mosm/kg)</td>
<td>22</td>
<td>511.77</td>
<td>202.83</td>
<td>521</td>
<td>174 - 951</td>
<td>250 - 750</td>
</tr>
<tr>
<td>Urinary sodium (mEq/L)</td>
<td>22</td>
<td>71.68</td>
<td>51.34</td>
<td>59</td>
<td>13 - 188</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>
SECTION 2: MULTIPLE REGRESSION ANALYSES

3.2.1 NORMALITY DISTRIBUTION OF DATA

Data was tested for normality using histograms and the Shapiro-Wilk test. The findings were interpreted with the assistance of a statistician. Parametric and non-parametric tests were used as appropriate.

3.2.2 MULTIPLE REGRESSION ANALYSIS OF THE IMPEDANCE INDEX (H²/R) (TABLE 17)

A multiple regression analysis was conducted to see which demographic factors independently predicted H²/R. The variables examined included the Burge-4 score (thirst, dry mouth, unpleasant taste and fatigue), age, ur:cr ratio, gender, presence of oedema, ECOG and the Morita dehydration score. Multiple linear regression analysis assumes that the residuals are not correlated serially from one observation to the next. The Durbin–Watson statistic is used in multiple linear regression to test whether the residuals are independent. The measured value is called ‘autocorrelation’ and suggests that recorded observations are similar. A value of 2 suggests that no autocorrelation (i.e. similarity between observations) exists within the sample. Values near 0 indicate positive autocorrelation whereas values toward 4 suggest negative autocorrelation. In this analysis, the value of Durbin-Waston was 1.74, approximately equal to 2, which suggests that no serial correlation was present in this analysis.

The R² indicates how well the data fits the statistical model. Overall these variables significantly predicted H²/R, F(7, 82) = 11.58, p<.001, R² = 0.50. This means that 50% of the variation of H²/R in this sample can be predicted by the variables included in this equation. In multiple regression analysis, the R² will automatically increase as more variables are added to the equation. The adjusted R² attempts to adjust for this phenomenon by only increasing when the added variable increases the R² more than expected by chance. Consequently, R² functions to quantify the relationship the linear relationship of data in the sample whereas the adjusted R² provides an estimate of the degree of relationship in the underlying population.
In this analysis the adjusted of $R^2$ score= 0.45 was close to the $R^2$; this suggests that there has been minimal shrinkage of the prediction model. Four variables were statistically significant in the prediction of impedance index. Female gender was associated with a 13.85 decrease in $H^2/R$ (p<.001). Each one point increase of the Morita dehydration score corresponded with a 2.55 (p=.02) decrease of $H^2/R$. Similarly, each one point increase of the Burge-4 score corresponded with a .29 (p=.04) decrease of $H^2/R$. These results suggest that the increasing values of the Burge-4 and Morita scores correspond with a decrease in TBW volume. The presence of oedema was associated with a 10.94 increase in $H^2/R$ (p<.001), which suggests increasing TBW volume.

### 3.2.3 MULTIPLE REGRESSION ANALYSIS OF THE BURGE-4 SCORE (TABLE 18)

A multiple linear regression analysis was undertaken to determine whether medications influenced the Burge-4 symptom analysis. The anticholinergic score, total daily morphine dose, the presence of diuretic medication and the use of SNRI/SSRI medications were entered into the regression equation.

The value of the Durbin-Waston was 2.01. This is approximately equal to 2, indicating that there is no serial correlation between the variables. These variables did not independently predict the Burge-4 score, $F(4, 84) = .975, p=.5321, R^2 = 0.04$. Here the $R^2$ value of .04 suggests that 4% of the variation of Burge-4 score can be predicted the medication variables. The adjusted $R^2$ score of -.006 was lower than the $R^2$, and suggests the prediction model for the sample has provided an overestimate of the (limited) relationship in the underlying population.
### TABLE 17: MULTIPLE REGRESSION ANALYSIS OF H²/R

<table>
<thead>
<tr>
<th>Variable</th>
<th>B (standard error)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>96.96 (10.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>.13 (.11)</td>
<td>.246</td>
</tr>
<tr>
<td>Female</td>
<td>-13.85 (2.52)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ECOG</td>
<td>-.55 (1.38)</td>
<td>.692</td>
</tr>
<tr>
<td>Oedema present</td>
<td>10.94 (2.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Urea:creatinine ratio</td>
<td>-.02 (.02)</td>
<td>.423</td>
</tr>
<tr>
<td>Morita dehydration score</td>
<td>-2.55 (1.1)</td>
<td>.023</td>
</tr>
<tr>
<td>Burge-4 score</td>
<td>-.29 (.14)</td>
<td>.038</td>
</tr>
<tr>
<td>R</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>R squared</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Adjusted R squared</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Standard error of estimate</td>
<td>11.58</td>
<td></td>
</tr>
<tr>
<td>Durbin-Watson</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>No. of observations</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 18: BURGE-4 LINEAR REGRESSION ANALYSIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>B (standard error)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>54.78 (9.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anticholinergic score</td>
<td>.86 (1.16)</td>
<td>.461</td>
</tr>
<tr>
<td>Daily morphine dose</td>
<td>.002 (0.19)</td>
<td>.936</td>
</tr>
<tr>
<td>Diuretic medication</td>
<td>-1.68 (4.65)</td>
<td>.719</td>
</tr>
<tr>
<td>SSRI or SNRI</td>
<td>-7.42 (4.42)</td>
<td>.097</td>
</tr>
<tr>
<td>R</td>
<td>.198</td>
<td></td>
</tr>
<tr>
<td>R squared</td>
<td>.039</td>
<td></td>
</tr>
<tr>
<td>Adjusted R squared</td>
<td>-.006</td>
<td></td>
</tr>
<tr>
<td>Standard error of estimate</td>
<td>15.45</td>
<td></td>
</tr>
<tr>
<td>Durbin-Watson</td>
<td>2.01</td>
<td></td>
</tr>
</tbody>
</table>

### 3.2.4 SUMMARY OF CHAPTER

Ninety patients (recruitment rate 76.3%) participated in the study. Our data describes a sample consisting of mainly Caucasian individuals with various cancer diagnoses of which lung was the most common primary cancer site affected. Overall, participants had an average age of 71, an ECOG performance status of 2 or 3 and a daily oral fluid intake of approximately 500 – 799mls. Pre-renal failure was present in 37 (41.1%) patients and mean eGFR was 72.1 ml/min/1.73m². The sample was heavily symptomatic, with the highest mean scores recorded for fatigue, dry mouth and thirst. The prevalence of dehydration related symptoms was very similar to the last study to use the Burge assessment tool to evaluate symptoms in a palliative cancer population.²⁵⁰ Although many patients received medications (i.e. opioids, diuretics, anticholinergics, SNRIs and SSRIs) known to cause the same symptoms evaluated in the Burge-4 score (i.e. dry mouth, thirst and fatigue and unpleasant taste) regression analysis demonstrates that these medications were not predictive of the Burge-4 score. Four variables (gender, oedema, Morita dehydration score and the Burge-4 score) significantly influenced
H^2/R. This may suggest that these factors are associated with (and can predict) TBW volume.
CHAPTER 4: THE USE OF BIVA TO COMPARE HYDRATION BETWEEN STUDY PARTICIPANTS AND REFERENCE POPULATIONS

4.1.1 INTRODUCTION

The baseline BIVA results of participants are reported in this chapter. The RXc graph was used to classify hydration status of individuals relative to a non-cancer reference population. Statistical analysis was conducted to test for differences between hydration states according to clinical observations, biochemistry and self-reported symptoms. Finally, the mean vectors for the entire sample were converted to Z-scores and compared to other cancer populations using the RXc Z-score graph.\(^{144}\)

4.1.2 BODY COMPOSITION CLASSIFICATION ACCORDING TO THE RXC GRAPH (TABLES 19 & 20; FIGURES 16 & 17)

The hydration status of subjects was classified using the RXc graph. No significant difference in hydration classification was evident between men and women. The majority of the sample was normally hydrated (n=43, 47.8%); with more-hydration more prevalent than less hydration.

TABLE 19: CLASSIFICATION OF HYDRATION AS A FIVE-ITEM SCALE ACCORDING TO THE RXC GRAPH

<table>
<thead>
<tr>
<th>Classification</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very less-hydrated</td>
<td>5</td>
<td>2</td>
<td>7 (7.8)</td>
<td>-</td>
</tr>
<tr>
<td>Less-hydrated</td>
<td>2</td>
<td>1</td>
<td>3 (3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>25</td>
<td>43 (47.8)</td>
<td>-</td>
</tr>
<tr>
<td>More-hydrated</td>
<td>6</td>
<td>10</td>
<td>16 (17.8)</td>
<td>-</td>
</tr>
<tr>
<td>Very more-hydrated</td>
<td>11</td>
<td>10</td>
<td>21 (23.3)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>48</td>
<td>90</td>
<td>.49</td>
</tr>
</tbody>
</table>
TABLE 20: CLASSIFICATION OF HYDRATION AS A THREE-ITEM SCALE ACCORDING TO THE RXC GRAPH SCALE

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18</td>
<td>25</td>
<td>43 (47.8)</td>
<td>-</td>
</tr>
<tr>
<td>Less-hydrated</td>
<td>7</td>
<td>3</td>
<td>10 (11.1)</td>
<td>-</td>
</tr>
<tr>
<td>More-hydrated</td>
<td>17</td>
<td>20</td>
<td>37 (41.1)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>48</td>
<td>90</td>
<td>.27</td>
</tr>
</tbody>
</table>

FIGURE 16: VECTOR POSITIONS FOR MALES ON THE RXC POINT GRAPH (N=42)

FIGURE 17: VECTOR POSITIONS FOR FEMALES ON THE RXC POINT GRAPH (N=48)
4.1.3 COMPARISON OF VARIABLES ACCORDING TO THE LESS-HYDRATED AND NOT LESS-HYDRATED GROUPS (TABLES 21 – 22)

The results of the hydration classification were simplified to compare less-hydrated patients (n=10, 11.1%) to those without less-hydration (n=80, 88.9%) (Table 21). Mann U Whitney (U) was used to analyse the ordinal scores of ECOG, the Morita Dehydration Score and the oral intake assessment. The Mann-Whitney test is non-parametric test that is used to evaluate differences between two ordinal samples by comparing the mean rank of each variable. The mean rank for oral intake was significantly higher in patients without less-hydration compared to those who were less-hydrated (U(90) =257.5, p=0.048). Significant differences in bio-impedance measurements were observable based on hydration status (Tables 22). Notably, the $H^2/R$ was significantly lower in less-hydration (M=39.57, SD=9.28 vs. M=53.08, SD=15.40; t(90)=-2.71, p=0.008). Phase angle was higher in less-hydration (M=6.11, SD=2.16) compared with other patients (M=4.53, SD=1.09); t(9.58)=2.27, p=0.047. Less-hydrated patients also had significantly higher values for R/H (t(88)=4.16, p<.001) and Xc/H (t(88)=7.82, p<.001) compared to all other patients.

Compared with the rest of the sample, less-hydrated individuals experienced higher scores for several variables; however, many of these items did not reach statistical significance. These included the Burge-4 score (M=257.6, SD=91.8 vs. M=217.6, SD=95.5; p=.21) the Morita dehydration score (U(90) = 269, p=.08), the ur:cr ratio (M=137.2, SD=101.3 vs. M=91.6, SD=42.2; p=.19), urine osmolality (M=540.5, SD=177.0 vs. M=505.4, SD=212.3; p=.35) and ECOG (M (326), p=.32). Sub-analysis of the Morita score demonstrated that axilla dryness was significantly higher in less-hydrated participants compared to those not less-hydrated (U(90)=245, p=0.02).
### TABLE 21: CLASSIFICATION OF LESS-HYDRATION ACCORDING TO THE RXC GRAPH

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less hydrated</td>
<td>7</td>
<td>3</td>
<td>10 (11.1)</td>
<td>-</td>
</tr>
<tr>
<td>Not less hydrated</td>
<td>35</td>
<td>45</td>
<td>80 (88.9)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>48</td>
<td>90</td>
<td>.18</td>
</tr>
</tbody>
</table>

### TABLE 22: COMPARISON BETWEEN LESS HYDRATED AND NOT LESS HYDRATED GROUPS ACCORDING TO SELF-REPORTED SYMPTOMS, BIOCHEMISTRY AND BIO-IMPEDANCE MEASUREMENTS

<table>
<thead>
<tr>
<th></th>
<th>Less hydrated (n=10)</th>
<th>All other patients (n=80)</th>
<th>T test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burge-4 score (mm)</td>
<td>Mean: 257.60, SD: 91.76</td>
<td>Mean: 217.63, SD: 95.47</td>
<td>1.25</td>
<td>.21</td>
</tr>
<tr>
<td>Thirst</td>
<td>Mean: 72.70, SD: 22.97</td>
<td>Mean: 54.04, SD: 29.67</td>
<td>1.92</td>
<td>.06</td>
</tr>
<tr>
<td>Pain</td>
<td>Mean: 45.50, SD: 39.42</td>
<td>Mean: 50.66, SD: 29.88</td>
<td>-0.50</td>
<td>.62</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Mean: 70.60, SD: 25.80</td>
<td>Mean: 58.69, SD: 31.07</td>
<td>1.16</td>
<td>.25</td>
</tr>
<tr>
<td>Nausea</td>
<td>Mean: 23.20, SD: 36.76</td>
<td>Mean: 25.91, SD: 30.76</td>
<td>-0.26</td>
<td>.80</td>
</tr>
<tr>
<td>Unpleasant taste</td>
<td>Mean: 52.20, SD: 37.51</td>
<td>Mean: 41.11, SD: 33.71</td>
<td>0.97</td>
<td>.34</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Mean: 62.10, SD: 23.73</td>
<td>Mean: 63.79, SD: 30.92</td>
<td>-0.17</td>
<td>.87</td>
</tr>
<tr>
<td>Pleasure in drinking</td>
<td>Mean: 60.89, SD: 30.58</td>
<td>Mean: 69.65, SD: 28.97</td>
<td>-0.86</td>
<td>.40</td>
</tr>
<tr>
<td>Ur:Cr ratio</td>
<td>Mean: 137.15, SD: 101.33</td>
<td>Mean: 91.62, SD: 42.20</td>
<td>1.41</td>
<td>.19</td>
</tr>
<tr>
<td>Na</td>
<td>Mean: 134.10, SD: 4.77</td>
<td>Mean: 136.38, SD: 4.17</td>
<td>-1.60</td>
<td>.11</td>
</tr>
<tr>
<td>eGFR</td>
<td>Mean: 71.00, SD: 24.68</td>
<td>Mean: 72.24, SD: 18.09</td>
<td>-0.20</td>
<td>.85</td>
</tr>
<tr>
<td>AdjCa</td>
<td>Mean: 2.26, SD: 0.13</td>
<td>Mean: 2.32, SD: 0.25</td>
<td>-0.81</td>
<td>.42</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>Mean: 281.75, SD: 18.46</td>
<td>Mean: 286.68, SD: 9.38</td>
<td>-0.95</td>
<td>.35</td>
</tr>
<tr>
<td>Albumin</td>
<td>Mean: 29.70, SD: 3.95</td>
<td>Mean: 32.36, SD: 6.25</td>
<td>-1.31</td>
<td>.19</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>Mean: 540.50, SD: 177.03</td>
<td>Mean: 505.39, SD: 212.25</td>
<td>.31</td>
<td>.76</td>
</tr>
<tr>
<td>Urine:plasma osmolality</td>
<td>Mean: 1.71, SD: 0.44</td>
<td>Mean: 1.71, SD: 0.73</td>
<td>-0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>Urinary Na</td>
<td>Mean: 69.75, SD: 67.02</td>
<td>Mean: 71.11, SD: 49.62</td>
<td>-0.08</td>
<td>.94</td>
</tr>
</tbody>
</table>
### 4.1.4 COMPARISON OF BIO-IMPEDANCE VECTORS ACCORDING TO CLINICAL OBSERVATIONS AND SELF-REPORTED SYMPTOMS (TABLE 23, FIGURES 18A-F)

BIVA demonstrated statistically significant differences according to several dichotomous variables, which were analysed on account of the presence or absence of each characteristic. This included assessment of the ‘less-hydrated’ status ($T^2=6.3, p<.001$), oedema ($T^2=12.1, p<.001$), thirst score cut-off of 50mm ($T^2=11.2, p<.001$), Morita dehydration cut-off of 2 ($T^2=33.6, p<.001$) and ECOG performance status cut-off of 2 ($T^2=6.7, p=.04$). These differences were further analysed with the RXc mean graph to determine their meaning.

<table>
<thead>
<tr>
<th></th>
<th>Less hydrated (n=10)</th>
<th>All other patients (n=80)</th>
<th>T test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>$H^2/R$</td>
<td>39.57</td>
<td>9.28</td>
<td>53.08</td>
<td>15.40</td>
</tr>
<tr>
<td>PA</td>
<td>6.11</td>
<td>2.16</td>
<td>4.53</td>
<td>1.09</td>
</tr>
<tr>
<td>RH</td>
<td>437.59</td>
<td>77.96</td>
<td>329.58</td>
<td>77.36</td>
</tr>
<tr>
<td>XcH</td>
<td>44.77</td>
<td>10.76</td>
<td>10.76</td>
<td>6.83</td>
</tr>
</tbody>
</table>

Less hydrated participants had higher values for R/H compared to those not less-hydrated ($T^2=6.3, p<.001$) (Figure 18a). This finding, coupled with the vector position, suggests lower TBW volume was present in less-hydrated individuals. The larger confidence ellipse in less-hydrated patients is possibly caused by the small number patients in the analysis (n=10). The mean impedance vector for oedematous participants was shorter with comparatively lower R/H values ($T^2=12.1, p<0.001$) (Figure 18b). Compared with non-oedematous individuals, the oedematous vector was more inferiorly placed, suggesting relatively higher TBW.

For thirst (sub-score of the Burge-4 score) R/H were higher for scores $\geq 50$mm compared to $< 50$mm ($T^2=11.2, p<0.001$). This suggests those with thirst scores $\geq 50$mm have lower TBW than those with scores $< 50$mm (Figure 18c). Morita dehydration scores of $\geq 2$ had higher R/H, suggesting less TBW, compared to individuals with scores $< 2$ ($T^2=33.6, p<.001$) (Figure 18d). Participants classified as
ECOG-4 had higher R/H, with a vector position that suggested less TBW, compared to an ECOG status of <4 ($T^2=6.7$, $p=.04$) (Figure 18e). Women had significantly higher R/H scores compared to men ($T^2=16.1$, $p<.001$) with a vector position (Figure 18f) suggesting comparatively lower TBW volumes in females compared to males.
<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>R/H Mean</th>
<th>R/H SD</th>
<th>Xc/H Mean</th>
<th>Xc/H SD</th>
<th>(R/H, Xc/H)</th>
<th>T*</th>
<th>F</th>
<th>D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less-hydrated</td>
<td>10</td>
<td>437.59</td>
<td>77.96</td>
<td>44.77</td>
<td>10.76</td>
<td>0.28</td>
<td>61.3</td>
<td>30.3</td>
<td>2.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Not less-hydrated</td>
<td>80</td>
<td>329.58</td>
<td>77.36</td>
<td>25.55</td>
<td>6.83</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>27</td>
<td>299.8</td>
<td>88.8</td>
<td>23.7</td>
<td>5.7</td>
<td>0.49</td>
<td>12.1</td>
<td>6</td>
<td>.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No oedema</td>
<td>63</td>
<td>359.5</td>
<td>76.1</td>
<td>29.4</td>
<td>10.3</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burge-4 ≥222mm</td>
<td>45</td>
<td>355.79</td>
<td>78.02</td>
<td>29.42</td>
<td>11.20</td>
<td>0.48</td>
<td>3.7</td>
<td>1.8</td>
<td>.41</td>
<td>.16</td>
</tr>
<tr>
<td>Burge-4 &lt;222mm</td>
<td>45</td>
<td>327.36</td>
<td>88.58</td>
<td>25.95</td>
<td>7.11</td>
<td>0.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thirst ≥50mm</td>
<td>52</td>
<td>365.1</td>
<td>83.6</td>
<td>29.6</td>
<td>10.6</td>
<td>0.48</td>
<td>11.2</td>
<td>5.5</td>
<td>.71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thirst &lt;50mm</td>
<td>38</td>
<td>309.4</td>
<td>74.8</td>
<td>25.1</td>
<td>7.0</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

The analysis compared differences between the vector means for each category (e.g. mean vectors of ‘less hydrated’ patients were directly compared to those ‘not-less hydrated’). The p-value is the statistical significance of the difference between the mean vectors.
FIGURE 18: RXC MEAN GRAPH DEMONSTRATING SIGNIFICANT DIFFERENCES IN BIVA FOR CATEGORICAL ANALYSES WITHIN THE SAMPLE (N=90)

Figure 18a: Less-hydrated (red ellipse); not less-hydrated (black ellipse). $T^2=6.3$, $p<.001$

Figure 18b: No oedema (red ellipse); oedema (black ellipse), $T^2=12.1$, $p<.001$

Figure 18c: Thirst score of ≥50mm (red ellipse); <50mm (black ellipse), $T^2=11.2$, $p<.001$.

Figure 18d: Morita score ≥2 (red ellipse); score <2 (black ellipse), $T^2=33.6$, $p<.001$. 
Figure 18e: ECOG stage 4 (red ellipse) and <4 (black ellipse), $T^2=6.7$, $p=.04$.

Figure 18f: females (red ellipse) and males (black ellipse), $T^2=16.4$, $p<.001$. 
4.1.5 GENDER SUB-ANALYSIS (TABLES 25 & 26; 19A-F & 20A-B)

Statistically significant vector differences were noted when the data was sub-analysed according to gender. Mean vectors were statistically significantly different in both genders (Figures 19a and 20a) according to the presence or absence of less-hydration (men, $T^2=56.9$, $p<.001$; females, $T^2=37.3$, $p<.001$) and the presence or absence of oedema (Figures 19b and 20b) (males, $T^2=15.7$, $p<0.001$; females, $T^2=3$, $p<0.001$).

The only other significant findings were evident in men. Males with dry mouth VAS scores $\geq 50$mm had higher values of R/H and similar Xc/H when compared to those with scores $<50$mm ($T^2=7.5$, $p=.04$) (Figure 19c). Although the mean vectors for dry mouth scores (cut off of 50mm) were significantly different from each other, these vectors were in a similar hydration position, according to the parallel divisions of the 5-point RXc graph (Figure 19c). Morita dehydration scores of $\geq 2$ (Figure 19d) had significantly higher mean R/H (suggesting lower TBW) compared to scores of $<2$ ($T^2=14.1$, $p<.003$).
<table>
<thead>
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<th>N</th>
<th>R/H Mean</th>
<th>R/H SD</th>
<th>Xc/H Mean</th>
<th>Xc/H SD</th>
<th>RH, XcH</th>
<th>T²</th>
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</tbody>
</table>
TABLE 25: BIVA ANALYSES FOR FEMALES ACCORDING TO SEVERAL CLINICAL VARIABLES (N=48)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>R/H Mean</th>
<th>R/H SD</th>
<th>Xc/H Mean</th>
<th>Xc/H SD</th>
<th>RH, XcH</th>
<th>T²</th>
<th>F</th>
<th>D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less-hydrated</td>
<td>3</td>
<td>482.24</td>
<td>80.23</td>
<td>53.84</td>
<td>17.82</td>
<td>0.99</td>
<td>37.3</td>
<td>18.3</td>
<td>3.64</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Not less-hydrated</td>
<td>43</td>
<td>364.86</td>
<td>75.23</td>
<td>27.43</td>
<td>6.42</td>
<td>0.450</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>17</td>
<td>334.85</td>
<td>89.99</td>
<td>23.88</td>
<td>5.34</td>
<td>0.56</td>
<td>11.3</td>
<td>5.5</td>
<td>1.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No oedema</td>
<td>31</td>
<td>392.68</td>
<td>66.93</td>
<td>31.94</td>
<td>10.39</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burge-4 ≥222mm (mean)</td>
<td>29</td>
<td>374.21</td>
<td>77.04</td>
<td>30.99</td>
<td>11.047</td>
<td>0.43</td>
<td>3.4</td>
<td>1.6</td>
<td>.54</td>
<td>.20</td>
</tr>
<tr>
<td>Burge-4 &lt;222mm (mean)</td>
<td>19</td>
<td>369.12</td>
<td>86.34</td>
<td>26.18</td>
<td>6.36</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thirst ≥50mm</td>
<td>32</td>
<td>382.95</td>
<td>82.73</td>
<td>30.64</td>
<td>10.68</td>
<td>0.42</td>
<td>3.8</td>
<td>1.9</td>
<td>.60</td>
<td>.17</td>
</tr>
<tr>
<td>Thirst &lt;50mm</td>
<td>16</td>
<td>342.70</td>
<td>67.13</td>
<td>25.98</td>
<td>6.55</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpleasant taste ≥50mm</td>
<td>22</td>
<td>386.83</td>
<td>76.15</td>
<td>30.17</td>
<td>7.65</td>
<td>0.49</td>
<td>1.4</td>
<td>.7</td>
<td>.34</td>
<td>50</td>
</tr>
<tr>
<td>Unpleasant taste &lt;50mm</td>
<td>26</td>
<td>359.82</td>
<td>82.51</td>
<td>28.16</td>
<td>11.20</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth ≥50mm</td>
<td>34</td>
<td>377.55</td>
<td>74.13</td>
<td>30.32</td>
<td>10.21</td>
<td>0.42</td>
<td>2.0</td>
<td>1.0</td>
<td>.45</td>
<td>.39</td>
</tr>
<tr>
<td>Dry mouth &lt;50mm</td>
<td>14</td>
<td>359.19</td>
<td>94.46</td>
<td>26.07</td>
<td>7.80</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue ≥50mm</td>
<td>36</td>
<td>379.12</td>
<td>73.97</td>
<td>28.42</td>
<td>6.70</td>
<td>0.49</td>
<td>3.3</td>
<td>1.6</td>
<td>.61</td>
<td>.21</td>
</tr>
<tr>
<td>Fatigue &lt;50mm</td>
<td>12</td>
<td>351.42</td>
<td>96.41</td>
<td>31.08</td>
<td>15.89</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretions</td>
<td>2</td>
<td>451.40</td>
<td>41.98</td>
<td>30.06</td>
<td>6.22</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No secretions</td>
<td>46</td>
<td>368.75</td>
<td>79.70</td>
<td>29.04</td>
<td>9.85</td>
<td>0.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morita dehydration ≥2</td>
<td>29</td>
<td>391.06</td>
<td>72.73</td>
<td>30.43</td>
<td>11.25</td>
<td>0.39</td>
<td>4.5</td>
<td>2.2</td>
<td>.63</td>
<td>.12</td>
</tr>
<tr>
<td>Morita dehydration &lt;2</td>
<td>19</td>
<td>343.41</td>
<td>83.83</td>
<td>27.04</td>
<td>6.40</td>
<td>0.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>N</td>
<td>R/H Mean</td>
<td>R/H SD</td>
<td>Xc/H Mean</td>
<td>Xc/H SD</td>
<td>RH, XcH</td>
<td>T2</td>
<td>F</td>
<td>D</td>
<td>P</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----</td>
<td>----------</td>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td>----</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Dry axilla</td>
<td>26</td>
<td>384.10</td>
<td>75.01</td>
<td>31.67</td>
<td>11.31</td>
<td>0.42</td>
<td>4.4</td>
<td>2.1</td>
<td>.61</td>
<td>.13</td>
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<tr>
<td>Moist axilla</td>
<td>22</td>
<td>358.13</td>
<td>85.07</td>
<td>26.03</td>
<td>6.30</td>
<td>0.51</td>
<td>2.8</td>
<td>1.4</td>
<td>.51</td>
<td>.26</td>
</tr>
<tr>
<td>Sunken eyes</td>
<td>17</td>
<td>387.08</td>
<td>68.47</td>
<td>32.16</td>
<td>13.09</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes not sunken</td>
<td>31</td>
<td>364.04</td>
<td>85.60</td>
<td>27.40</td>
<td>6.88</td>
<td>0.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ur:Cr ≥100:1</td>
<td>22</td>
<td>372.76</td>
<td>93.77</td>
<td>30.68</td>
<td>13.02</td>
<td>0.46</td>
<td>1.3</td>
<td>0.7</td>
<td>.33</td>
<td>.52</td>
</tr>
<tr>
<td>Ur:Cr &lt;100:1</td>
<td>26</td>
<td>371.72</td>
<td>68.12</td>
<td>27.73</td>
<td>5.46</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG ≥2</td>
<td>38</td>
<td>376.4</td>
<td>87.7</td>
<td>29.0</td>
<td>10.7</td>
<td>0.46</td>
<td>.8</td>
<td>.4</td>
<td>.32</td>
<td>.68</td>
</tr>
<tr>
<td>ECOG&lt;2</td>
<td>10</td>
<td>356.3</td>
<td>37.6</td>
<td>29.6</td>
<td>4.7</td>
<td>0.49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG ≥3</td>
<td>29</td>
<td>380.2</td>
<td>96.7</td>
<td>28.9</td>
<td>11.8</td>
<td>0.50</td>
<td>1.2</td>
<td>.6</td>
<td>.32</td>
<td>.57</td>
</tr>
<tr>
<td>ECOG&lt;3</td>
<td>19</td>
<td>359.9</td>
<td>43.5</td>
<td>29.4</td>
<td>5.3</td>
<td>0.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG =4</td>
<td>11</td>
<td>411.5</td>
<td>60.7</td>
<td>31.9</td>
<td>16.6</td>
<td>0.17</td>
<td>3.7</td>
<td>1.8</td>
<td>.66</td>
<td>.17</td>
</tr>
<tr>
<td>ECOG &lt;4</td>
<td>37</td>
<td>360.5</td>
<td>82.0</td>
<td>28.2</td>
<td>6.5</td>
<td>0.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral intake ≥800mls</td>
<td>13</td>
<td>340.56</td>
<td>69.61</td>
<td>29.45</td>
<td>6.84</td>
<td>0.61</td>
<td>4.1</td>
<td>2</td>
<td>.66</td>
<td>.15</td>
</tr>
<tr>
<td>Oral intake &lt;800mls</td>
<td>35</td>
<td>383.95</td>
<td>81.29</td>
<td>28.95</td>
<td>10.64</td>
<td>0.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 19: RXC MEAN GRAPH DEMONSTRATING SIGNIFICANT DIFFERENCES IN BIVA FOR CATEGORICAL ANALYSES FOR MALES (N=42)

Figure 19a: Less-hydrated (red ellipse); not less-dehydrated (black ellipse). $T^2=56.9$, $p<0.001$

Figure 19b: No oedema (red ellipse); oedema (black ellipse), $T^2=15.7$, $p<0.001$

Figure 19c: Dry mouth score of $\geq 50\text{mm}$ (red ellipse); $<50\text{mm}$ (black ellipse), $T^2=7.5$, $p=.04$.

Figure 19d: Morita dehydration score $\geq 2$ (red ellipse); $<2$ (black ellipse), $T^2=14.1$, $p=0.003$. 


**Figure 20a**: Less-hydrated (red ellipse); not less-hydrated (black ellipse). $T^2=37.3$, $p<0.001$.

**Figure 20b**: No oedema (red ellipse); oedema (black ellipse), $T^2=12.1$, $p<0.001$.

\*vi The Less-hydrated (red ellipse) extends beyond the parameters of the figure.
4.1.6 THE RXC Z-SCORE GRAPH ANALYSIS (TABLE 26 & FIGURE 21)

Analysis from the RXc Z-score graph demonstrates that participants from this study were normally hydrated with a low muscle mass. Male and females were similarly placed within the 50% tolerance ellipse. Compared with previous results, our data was similar to the lung cancer samples reported by Toso et al.; however, breast cancer patients had more muscle mass and those affected by cancers of the head and neck cancer were leaner. The head and neck cancer studies show a slight difference in positions on the Z-score graph, with the sample populations respectively placed in the 50% and 75% tolerance ellipses.
<table>
<thead>
<tr>
<th>Author</th>
<th>Description</th>
<th>Study population details</th>
<th>Reference population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R/H Mean</td>
<td>Xc/H Mean</td>
</tr>
<tr>
<td>Nwosu 2014</td>
<td>Males, predominantly Caucasian, mixed advanced cancer (n=42)</td>
<td>306.6</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td>Female, predominantly Caucasian, mixed advanced cancer (n=48)</td>
<td>372.2</td>
<td>29.1</td>
</tr>
<tr>
<td>Toso 2000</td>
<td>Males, Caucasian, lung cancer stage IIIB (n=33)</td>
<td>302.0</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>Males, Caucasian, lung cancer stage IV (n=30)</td>
<td>314.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Malecka-Massalska 2012</td>
<td>Females, breast cancer (n=34)</td>
<td>377.54</td>
<td>53.58</td>
</tr>
<tr>
<td>Toso 2003</td>
<td>Males, Caucasian, lung cancer, locally advanced and disseminated (n=61)</td>
<td>317</td>
<td>26</td>
</tr>
<tr>
<td>Melecka Massala 2012</td>
<td>Males, head and neck cancer (n=56)</td>
<td>342.54</td>
<td>27.62</td>
</tr>
<tr>
<td>Toso 2003</td>
<td>Males, Caucasian, lung cancer in remission (n=31)</td>
<td>287</td>
<td>25</td>
</tr>
<tr>
<td>Melecka Massala 2013</td>
<td>Males, head and neck cancer (n=67)</td>
<td>327.01</td>
<td>28.04</td>
</tr>
</tbody>
</table>
FIGURE 21: RXC Z-SCORE GRAPH ANALYSIS FROM THIS STUDY AND PREVIOUS CANCER STUDIES FROM THE LITERATURE PRESENTED WITH THEIR REFERENCE POPULATIONS

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>●</td>
<td>Males, predominantly Caucasian, mixed advanced cancer (n=42), Nwosu et al 2014.</td>
</tr>
<tr>
<td>▲</td>
<td>Female, predominantly Caucasian, mixed advanced cancer (n=48), Nwosu et al 2014.</td>
</tr>
<tr>
<td>■</td>
<td>Males, Caucasian, lung cancer stage IIIb (n=33), Toso 2000.¹⁵⁸</td>
</tr>
<tr>
<td>○</td>
<td>Males, Caucasian, lung cancer stage IV (n=30), Toso 2000.¹⁵⁸</td>
</tr>
<tr>
<td>△</td>
<td>Females, breast cancer (n=34), Malecka-Massalska et al 2012.²⁹⁷</td>
</tr>
<tr>
<td>◆</td>
<td>Males, Caucasian, lung cancer, locally advanced and disseminated (n=61), Toso 2003.⁹⁸</td>
</tr>
<tr>
<td>□</td>
<td>Males, head and neck cancer (n=56), Melecka Massala 2012.²⁰⁶</td>
</tr>
<tr>
<td>×</td>
<td>Males, Caucasian, lung cancer in remission (n=31), Toso 2003.⁹⁸</td>
</tr>
<tr>
<td>◊</td>
<td>Males, head and neck cancer (n=67), Melecka Massala 2013.²⁹⁸</td>
</tr>
</tbody>
</table>
4.1.7 SUMMARY OF CHAPTER

The majority of this sample were normally hydrated (n=43, 47.8%), with more-hydration (n=37, 41.1%) more prevalent than less-hydration (n=10, 11.1%). Comparison between less-hydrated and those without less-hydration demonstrates that oral fluid intake was statistically significantly lower in less-hydrated participants (p=.048); additionally, axilla dryness (as measured by the Morita dehydration score) was significantly higher in less-hydration (p=.02). No other statistically significant differences were detected for the current sample. Although differences between these groups were not statistically significant, the analysis demonstrates that (when compared to those without less-hydration) individuals with less-hydration experienced higher values for several variables. This included the Burge-4 score (and its constituent items of thirst, dry mouth and unpleasant taste), the Morita dehydration score (and its constituent item of mucous membrane sub-score), ur:cr, urinary osmolality and ECOG performance status.

Overall, for the sample (n=90), BIVA demonstrates significant differences between mean vectors for those classified by the presence or absence of less-hydration (p<.001), oedema (p<.001), thirst VAS cut off of 50mm (p<.001), Morita dehydration score cut-off of 2 (p<.001) and ECOG cut off of 4 (p=.04). Women had less TBW volume compared to men and other variations in the significance of differences were present on account of gender. BIVA comparison with other cancer populations demonstrated that patients in this sample were normally hydrated (through placement within the normal 50% tolerance ellipse) and had a similar body composition to those affected by cancers of the lung and head and neck.
CHAPTER 5: SURVIVAL ANALYSIS

5.1.1 INTRODUCTION

Survival outcomes for study participants (according to hydration states, H2/R and biochemistry) are presented in this chapter. A cox regression analysis is described to illustrate the influence of confounding factors on survival. Throughout this chapter 95% confidence intervals are presented in square brackets.

5.1.2 DEMOGRAPHICS OF SURVIVAL DATA (TABLE 27 & 28)

Survival was recorded from the date of initial BIVA assessment. Each patient was followed up for 3 months at the end of data collection. Overall, 76 (84.4%) participants died, with 14 (15.6%) alive at the end of the follow-up period (Table 27). From the date of recruitment, 23 (25.6%) patients died within 30 days and four (4.4%) died within seven days. No patients were lost to follow-up. Median survival was 62 days [38.76, 85.24] and ranged between 2 to 410 days (Table 28).

TABLE 27: NUMBER OF PATIENTS ALIVE OR DECEASED ACCORDING TO 3-MONTH FOLLOW-UP, 30-DAY SURVIVAL AND 7-DAY SURVIVAL PERIODS

<table>
<thead>
<tr>
<th>Status</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients dead at the end of the 3 month</td>
<td>76</td>
<td>84.4</td>
</tr>
<tr>
<td>follow up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients alive at the end of the 3 month</td>
<td>14</td>
<td>15.6</td>
</tr>
<tr>
<td>follow up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients dead ≤30 days of study recruitment</td>
<td>23</td>
<td>25.6</td>
</tr>
<tr>
<td>Patients dead after ≤7 days of study</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>recruitment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 28: SURVIVAL TIME (DAYS) FOR THE SAMPLE (N=90) FROM THE DATE OF THE INITIAL ASSESSMENT

<table>
<thead>
<tr>
<th>Meana Estimate</th>
<th>SE</th>
<th>95% Confidence Interval Lower</th>
<th>95% Confidence Interval Upper</th>
<th>Median Estimate</th>
<th>SE</th>
<th>95% Confidence Interval Lower</th>
<th>95% Confidence Interval Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>108.634</td>
<td>12.264</td>
<td>84.597</td>
<td>132.671</td>
<td>62.000</td>
<td>11.859</td>
<td>38.757</td>
<td>85.243</td>
</tr>
</tbody>
</table>

a. Estimation is limited to the largest survival time if it is censored.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Survival time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>94.29</td>
</tr>
<tr>
<td>Median</td>
<td>64.00</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>86.38</td>
</tr>
<tr>
<td>Minimum</td>
<td>2</td>
</tr>
<tr>
<td>Maximum</td>
<td>410</td>
</tr>
</tbody>
</table>

5.1.3 SURVIVAL ANALYSIS OF PARTICIPANTS BASED ON THEIR HYDRATION STATUS CLASSIFICATION (TABLE 29, FIGURE 22)

Kaplan-Meier analysis of the three hydration states (normal, less-hydrated and more-hydrated) demonstrated that median survival was shortest at 44 days [34.7, 53.29] in less-hydration, followed by 68 days [19.28, 116.72] in normal hydration and 70 days [0, 141.8] in more-hydration. Log rank test of these three variables failed to demonstrate a statistically significant difference between the three categories (p=.09).
### TABLE 29: MEAN AND MEDIANS FOR SURVIVAL TIME ACCORDING TO THE THREE HYDRATION CLASSIFICATIONS

<table>
<thead>
<tr>
<th>Hydration classification according to BIVA</th>
<th>Mean&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Median</th>
<th>95% Confidence Interval</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Normal</td>
<td>110.614</td>
<td>18.483</td>
<td>74.388</td>
<td>146.840</td>
</tr>
<tr>
<td>Less hydrated</td>
<td>50.000</td>
<td>7.967</td>
<td>34.385</td>
<td>65.615</td>
</tr>
<tr>
<td>More hydrated</td>
<td>123.075</td>
<td>17.935</td>
<td>87.922</td>
<td>158.227</td>
</tr>
<tr>
<td>Overall</td>
<td>108.634</td>
<td>12.264</td>
<td>84.597</td>
<td>132.671</td>
</tr>
</tbody>
</table>

**Overall Comparisons**

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>4.926</td>
<td>2</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions for the different hydration classification according to BIVA.

**FIGURE 22: KAPLAN-MEIER GRAPH SHOWING SURVIVAL TIME IN DAYS ACCORDING TO THE THREE HYDRATION CLASSIFICATIONS AS DETERMINED BY BIVA (P=0.09)**

![Kaplan-Meier Graph](image-url)

*Modified impedance classification:
- Normal
- Less hydrated
- More hydrated
- Normal corrected
- Less hydrated-corrected
- More hydrated-corrected*
5.1.3.1 SURVIVAL ANALYSIS OF LESS HYDRATED VS. NOT LESS HYDRATED PATIENTS (TABLE 30, FIGURE 23)

As the median survival times for the normal and more-hydrated group were similar, these categories were combined to facilitate comparison between less-hydrated and those without less-hydration. Analysis of this variable demonstrates that median survival was statistically shorter in less-hydrated patients compared to other patients (44 days [34.7, 53.29] vs 68 days [36.84, 99.16], log-rank p=.04.

**TABLE 30: MEAN AND MEDIANS OF SURVIVAL TIMES ACCORDING TO THE LESS-HYDRATED BIVA CLASSIFICATION**

<table>
<thead>
<tr>
<th>Is the patient less-hydrated?</th>
<th>Mean</th>
<th>95% Confidence Interval</th>
<th>Median</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>No</td>
<td>115.964</td>
<td>13.543</td>
<td>89.419</td>
<td>142.508</td>
</tr>
<tr>
<td>Yes</td>
<td>50.000</td>
<td>7.967</td>
<td>34.385</td>
<td>65.615</td>
</tr>
<tr>
<td>Overall</td>
<td>108.634</td>
<td>12.264</td>
<td>84.597</td>
<td>132.671</td>
</tr>
</tbody>
</table>

**Overall Comparisons**

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>4.075</td>
<td>1</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions according to dehydration status classification.
FIGURE 23: KAPLAN-MEIER GRAPH SHOWING SURVIVAL TIME IN DAYS ACCORDING TO THE LESS-HYDRATED CLASSIFICATION AS DETERMINED BY BIVA (P=0.04)

5.1.3.2 SURVIVAL ANALYSIS OF MORE-HYDRATED VS. NOT MORE-HYDRATED PATIENTS (TABLE 31, FIGURE 24)

Median survival was longer in patients classified as more-hydrated compared to those who were not (49 days [23.14, 74.86] vs. 70 days [0, 141.8]); however, this difference was not statistically significant (p=.16).

TABLE 31: MEAN AND MEDIANS FOR SURVIVAL TIMES ACCORDING TO THE MORE-HYDRATED BIVA CLASSIFICATION

<table>
<thead>
<tr>
<th>Is the patient over-hydrated according to BIVA?</th>
<th>Mean</th>
<th>95% Confidence Interval</th>
<th>Median</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>No</td>
<td>99.177</td>
<td>15.411</td>
<td>68.971</td>
<td>129.383</td>
</tr>
<tr>
<td>Yes</td>
<td>123.075</td>
<td>17.935</td>
<td>87.922</td>
<td>158.227</td>
</tr>
<tr>
<td>Overall</td>
<td>108.634</td>
<td>12.264</td>
<td>84.597</td>
<td>132.671</td>
</tr>
</tbody>
</table>
5.1.3.3 SURVIVAL ANALYSIS ACCORDING TO $H^2/R$ (TABLE 32)

Cox regression analysis was conducted using $H^2/R$ as a continuous variable. The impedance index was a statically significant predictor of survival, HR=0.98 [.96, .99], $p=0.01$. Each unit $m^2$/Ohm increase of $H^2/R$ reduces the probability of death by a factor of 1.03 (i.e. $1/\text{Exp}[B]$). This suggests that a higher $H^2/R$ (which indicates higher TBW volumes) reduces the likelihood of death.
TABLE 32: COX REGRESSION ANALYSIS FOR H²/R

<table>
<thead>
<tr>
<th>Omnibus Tests of Model Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 Log Likelihood</td>
</tr>
<tr>
<td>Chi-square</td>
</tr>
<tr>
<td>562.690</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>H²/R</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariate Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>H²/R</td>
</tr>
</tbody>
</table>

5.1.4 SURVIVAL ANALYSIS ACCORDING TO RENAL BIOCHEMISTRY (TABLE 33 & 34, FIGURE 25)

Kaplan-Meier analysis demonstrates that participants with pre-renalfailure (ur:cr ratio ≥100:1) had significantly shorter median survival compared to those without (44 days [32.08, 55.92] vs. 100 days [48.51, 151.49], p=.03). Furthermore, cox regression analysis of the ur:cr ratio (as a continuous variable) provided a hazard ratio (HR) of 1.009 [1.005, 1.014], p=.003 (Table 34). This suggests that each unit increase (mmol:mmol) of the ur:cr ratio causes survival to worsen by a factor of 1.009.
TABLE 33: MEAN AND MEDIANS FOR SURVIVAL TIMES ACCORDING TO THE PRESENCE OF PRE-Renal FAILURE

<table>
<thead>
<tr>
<th>Is pre-renal failure present?</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>No</td>
<td>134.353</td>
<td>16.855</td>
</tr>
<tr>
<td>Yes</td>
<td>64.709</td>
<td>10.810</td>
</tr>
<tr>
<td>Overall</td>
<td>108.634</td>
<td>12.264</td>
</tr>
</tbody>
</table>

**Overall Comparisons**

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>8.987</td>
<td>1</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions according to the presence or absence of pre-renal failure.

FIGURE 25: KAPLAN-MEIER GRAPH SHOWING SURVIVAL TIME IN DAYS ACCORDING TO THE PRESENCE, OR ABSENCE, OF PRE-Renal FAILURE (P=.003)
### TABLE 34: COX REGRESSION SURVIVAL ANALYSIS ACCORDING TO THE UR:CR RATIO

<table>
<thead>
<tr>
<th>Omnibus Tests of Model Coefficientsa</th>
<th>Overall (score)</th>
<th>Change From Previous Step</th>
<th>Change From Previous Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 Log Likelihood</td>
<td>Chi-square</td>
<td>df</td>
<td>Sig.</td>
</tr>
<tr>
<td>555.675</td>
<td>15.867</td>
<td>1</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ur:Cr ratio</td>
<td>.009</td>
<td>.002</td>
<td>15.980</td>
<td>1</td>
<td>.000</td>
<td>1.009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariate Means</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ur:Cr ratio</td>
<td>96.683</td>
</tr>
</tbody>
</table>

### 5.1.5 ADJUSTMENT FOR POTENTIAL CONFOUNDERS USING COX REGRESSION ANALYSIS (TABLE 35)

Cox regression analysis was undertaken to evaluate the potential influence of confounding factors on survival. The equation included age (continuous), sex (dichotomous), ECOG performance status (ordinal), presence of metastatic disease (dichotomous), ur:cr ratio (continuous), and $H^2/R$ (continuous) and the less-hydrated classification (dichotomous).

Following adjustment, the $H^2/R$ (HR=0.97 [.95, .99]; p=0.003) and ur:cr (HR=1.009 [1.003, 1.015]; p=0.002), remained significant predictors of survival. Other factors were found to significantly influence survival. This included performance status, which was demonstrated by successive increases in the hazard ratios according to the ECOG grades. Comparatively, using ECOG-1 a reference, the risk of death increased by twofold for ECOG-2 (HR=2.64 [1.17, 5.94]; p=0.02) and by threefold in the ECOG-3 (HR=3.33 [1.50, 7.42]; p=0.003) and ECOG-4 (HR=3.35 [1.37, 8.21]; p=.008) grades respectively. Metastatic disease increased the risk of death by roughly twofold (HR=1.98 [1.15, 3.43]; p=.014). Following adjustment, the less-hydrated classification was no longer a statistically significant predictor of survival. Age and gender were not significant predictors of survival.
TABLE 35: COX REGRESSION SURVIVAL ANALYSIS FOR SEVERAL VARIABLES

<table>
<thead>
<tr>
<th>Omnibus Tests of Model Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>-2 Log Likelihood</strong></td>
</tr>
<tr>
<td>Chi-square</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>530.451</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>AGE</td>
</tr>
<tr>
<td>FEMALE</td>
</tr>
<tr>
<td>ECOG</td>
</tr>
<tr>
<td>ECOG (2 vs 1)</td>
</tr>
<tr>
<td>ECOG (3 vs 1)</td>
</tr>
<tr>
<td>ECOG (4 vs 1)</td>
</tr>
<tr>
<td>METASTASES</td>
</tr>
<tr>
<td>Ur:cr</td>
</tr>
<tr>
<td>LESS HYDRATED</td>
</tr>
<tr>
<td>H²/R</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariate Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
</tr>
<tr>
<td>SEX</td>
</tr>
<tr>
<td>ECOG (2 vs 1)</td>
</tr>
<tr>
<td>ECOG (3 vs 1)</td>
</tr>
<tr>
<td>ECOG (4 vs 1)</td>
</tr>
<tr>
<td>METASTASES</td>
</tr>
<tr>
<td>Ur:cr</td>
</tr>
<tr>
<td>LESS HYDRATED</td>
</tr>
<tr>
<td>H²/R</td>
</tr>
</tbody>
</table>

5.1.6 SUMMARY OF CHAPTER

Seventy-six (84.4%) participants died before the end of the follow-up period. Those who were classified as less-hydrated had statistically significant shorter survival compared to those who did not. Overall, survival was shortest in less-hydrated patients, longest in more hydration, with the survival for those normally-hydrated...
in between those two groups. Those who were classified with pre-renal failure had shorter survival compared to those who did not. Increasing H2/R value (suggesting higher TBW volume) was associated with longer survival and increasing ur:cr ratio (suggesting worsening renal function) was associated with shorter survival. Cox regression analysis identified potential confounding factors of metastatic disease and performance status. Following adjustment for these factors H2/R and ur:cr ratio still remained statistically significant predictors of survival. However, the less-hydrated classification was no longer a statistically significant predictor of survival following the regression analysis.
CHAPTER 6: EVALUATION OF LONGITUDINAL CHANGES IN HYDRATION THROUGH THE ANALYSIS OF REPEAT BIO-IMPEDANCE ASSESSMENTS

6.1.1 INTRODUCTION

This chapter presents analysis of participants receiving multiple assessments. The assessment frequency is presented in addition to an analysis of the influence of time-related changes of bio-impedance on survival.

6.1.2 NUMBER OF REPEAT ASSESSMENTS (TABLES 10 AND 37; FIGURES 26 & 27)

A total 126 assessments were conducted. Sixty-six (73.3%) patients were evaluated at baseline only whereas 24 (26.7%) received multiple assessments. Further information of the number of assessments is provided in table 10.

Of the participants receiving repeat assessments the RXc graph demonstrates that 15 (62.5%) were normally hydrated, eight (33.3%) were more-hydrated and one (4.2%) was less-hydrated. The final hydration classifications for the sample receiving repeat assessments were similar to baseline (Table 36). However, when compared to the baseline hydration status for all patients, a higher proportion of patients receiving repeat assessments were comparatively more likely to be normally hydrated (62.5% vs 47.8%) and less likely to be less-hydrated (4.2% vs. 11.1%) (see Table 20).
TABLE 36: COMPARISON OF HYDRATION STATUS CHARACTERISTICS OF THE BASELINE AND FINAL BIO-IMPEDANCE MEASUREMENTS IN PATIENTS RECEIVING MULTIPLE ASSESSMENTS

<table>
<thead>
<tr>
<th></th>
<th>Baseline assessment</th>
<th>Final assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>16</td>
<td>66.7</td>
</tr>
<tr>
<td>Less-hydrated</td>
<td>2</td>
<td>8.3</td>
</tr>
<tr>
<td>More-hydrated</td>
<td>6</td>
<td>25.0</td>
</tr>
</tbody>
</table>

6.1.3 PAIRED DATA ANALYSIS OF THE BASELINE AND FINAL BIO-IMPEDANCE (TABLE 37; FIGURES 28A, 28B & 28C)

The analysis of participants’ paired vectors analysis demonstrated that, when compared to baseline measurements, repeat BIVA assessments had lower (negative) Xc/H scores and higher values for R/H. The final vector difference position (Figure 28a) had moved down and right and has a 95% confidence ellipse that does not cross the origin (i.e. 0,0). Paired Hotelling’s $T^2$ test demonstrated that the paired vector difference was statistically significant ($T^2 = 9.5, <.001$). The higher dR/H suggested lower TBW on the final assessment compared to the first. The lower dXc/R suggested individuals had increased cellular breakdown on the final assessment compared to baseline. Sub-analysis by gender (Figure 28b & 28c), demonstrated similar results for women (p<.001). However, in men the vector difference demonstrated comparatively higher mean values for dR/H and dXc/H, which is represented by the mean vector moving upwards and right of the origin on the RXc graph (Figure 28b). This paired vector has a larger 95% confidence ellipse and is not a statistically significant finding (p=.5).
TABLE 37: RESULTS OF THE VECTOR DIFFERENCE ANALYSIS (BASELINE AND FINAL BIVA ASSESSMENTS)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>dr/H Mean</th>
<th>dr/H SD</th>
<th>dRc/H Mean</th>
<th>dRc/H SD</th>
<th>Correlation r (dR/H, dXc/H)</th>
<th>T^2</th>
<th>F</th>
<th>D</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24</td>
<td>14.3</td>
<td>33.4</td>
<td>-1.4</td>
<td>7.7</td>
<td>0.50</td>
<td>9.5</td>
<td>4.5</td>
<td>0.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Males</td>
<td>9</td>
<td>17.6</td>
<td>37.5</td>
<td>1.1</td>
<td>8.0</td>
<td>0.47</td>
<td>2</td>
<td>0.9</td>
<td>0.47</td>
<td>.5</td>
</tr>
<tr>
<td>Females</td>
<td>15</td>
<td>12.4</td>
<td>31.8</td>
<td>-3.0</td>
<td>7.4</td>
<td>0.52</td>
<td>9.8</td>
<td>4.5</td>
<td>0.81</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

FIGURE 26: RXC GRAPH SHOWING THE BASELINE AND FINAL BIO-IMPEDANCE VECTOR POSITIONS OF MALES RECEIVING MULTIPLE ASSESSMENTS (N= 9)

FIGURE 27: RXC GRAPH SHOWING THE BASELINE AND FINAL BIO-IMPEDANCE VECTOR POSITIONS OF FEMALES RECEIVING MULTIPLE ASSESSMENTS
FIGURE 28A: RXC PAIRED GRAPH DEMONSTRATING THE CHANGE IN VECTOR POSITION OF THE FIRST AND LAST BIVA ASSESSMENTS IN ALL PATIENTS RECEIVING REPEAT ASSESSMENTS (N=24)

FIGURE 28B: RXC PAIRED GRAPH DEMONSTRATING THE CHANGE IN VECTOR POSITION OF THE FIRST AND LAST BIVA ASSESSMENTS IN MALES RECEIVING REPEAT ASSESSMENTS (N=9)

FIGURE 28C: RXC PAIRED GRAPH DEMONSTRATING THE CHANGE IN VECTOR POSITION OF THE FIRST AND LAST BIVA ASSESSMENTS IN FEMALES RECEIVING REPEAT ASSESSMENTS (N=15)
6.1.4 ANALYSIS OF THE UR:CR RATIO AND H²/R CHANGE FROM BASELINE TO FINAL ASSESSMENT (TABLE 38)

An increase of the ur:cr ratio (from baseline to final assessment) was observed in twelve (50%) of the patients receiving repeat assessments, whereas an equal number (n=12, 50%) had no change or decrease in ur:cr ratio. The H²/R increased in nine (37.5%) patients between baseline and final assessments, with H²/R remaining the same or decreasing in 15 (62.5%).

TABLE 38: CHANGE IN THE UR:CR RATIO AND H²/R FROM BASELINE TO FINAL BIVA ASSESSMENT FOR PATIENTS RECEIVING MULTIPLE ASSESSMENTS

<table>
<thead>
<tr>
<th></th>
<th>Change in Ur:Cr ratio</th>
<th>Change in H²/R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>No change or decrease</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>Increase</td>
<td>12</td>
<td>50</td>
</tr>
</tbody>
</table>

6.1.5 SURVIVAL ANALYSIS (TABLE 39 & 40; FIGURES 29 & 30)

Kaplan Meier survival demonstrated no significant difference based on an increase or decrease of H²/R or ur:cr ratio from baseline to the final assessment.
TABLE 39: MEAN AND MEDIANS FOR SURVIVAL TIMES BASED ON THE CHANGE OF $H^2/R$ FROM BASELINE TO THE FINAL ASSESSMENT

<table>
<thead>
<tr>
<th>Is there an increase in $H^2/R$?</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>111.267</td>
<td>23.494</td>
</tr>
<tr>
<td>Yes</td>
<td>141.222</td>
<td>31.350</td>
</tr>
<tr>
<td>Overall</td>
<td>123.198</td>
<td>19.338</td>
</tr>
</tbody>
</table>

Overall Comparisons

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>.350</td>
<td>1</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions times based on the change of impedance index from baseline to final assessment.

FIGURE 29: KAPLAN-MEIER GRAPH SHOWING SURVIVAL TIME IN DAYS ACCORDING TO CHANGE IN $H^2/R$ (P=0.55)
### TABLE 40: MEAN AND MEDIANS FOR SURVIVAL TIMES BASED ON THE CHANGE OF UR:CR RATIO FROM BASELINE TO FINAL ASSESSMENT

<table>
<thead>
<tr>
<th>Change in Ur:Cr</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>No change or decrease</td>
<td>112.750</td>
<td>24.753</td>
</tr>
<tr>
<td>Increase</td>
<td>135.250</td>
<td>31.317</td>
</tr>
<tr>
<td>Overall</td>
<td>123.198</td>
<td>19.338</td>
</tr>
</tbody>
</table>

**Overall Comparisons**

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>.864</td>
<td>1</td>
</tr>
</tbody>
</table>

*Test of equality of survival distributions for the different levels of Change in Ur:Cr.*

**FIGURE 30: KAPLAN-MEIER GRAPH SHOWING SURVIVAL IN DAYS ACCORDING TO CHANGE IN UR:CR RATIO (p=0.35)**

![Kaplan-Meier Graph](image)
6.1.6 SUMMARY OF CHAPTER

In total, twenty-four (26.7%) participants received multiple assessments. When compared to the baseline assessments for all participants, those receiving repeated measurements were more likely to be normally-hydrated and less likely to be less-hydrated. Compared to baseline, the paired vector analysis demonstrated the dR/H was statistically significantly higher (suggesting less hydration) and lower Xc/R (suggesting less cellular mass) on the final assessment. This finding remained statistically significant in females but not in men which may suggest possible variance by gender. An increase or decrease of H²/R or ur:cr ratio did not significantly influence survival.
CHAPTER 7: DISCUSSION

SECTION 1: OVERVIEW OF RESEARCH PROJECT

This project was devised to improve the understanding of hydration in advanced cancer patients, in order to contribute new knowledge to the evidence base. It is hoped that this thesis will lead to further work which will eventually lead to improvements in patient care.

The key results from the study are examined in section 7.2.1 and are discussed in relation to the study objectives. The strengths and weaknesses of the study are presented in sections 7.2.2 and 7.2.3 respectively. The contribution to the evidence base is discussed in section 7.3.2 with the concluding remarks presented in section 7.3.4.

7.1.1 RATIONALE FOR THESIS AND GAP IN KNOWLEDGE

The aims and objectives in this study were developed to add new knowledge about the subject of hydration in advanced cancer. The gap in evidence can be summarised by the following points:

- There is limited understanding of how hydration in advanced cancer influences symptoms, physical signs and biochemical tests. To date, no studies have used bio-impedance measurements in advanced cancer to evaluate differences in hydration according to these factors.

- The difference in body composition and hydration status between different types of cancer is not clearly understood. To date, no studies have used the BIVA Z-score analysis to synthesize data for cancer studies in order to compare for differences in hydration.

- There is limited data to describe how hydration influences survival in advanced cancer. There are no studies to determine whether hydration (classified by BIVA or H²/R) is predictive of survival in advanced cancer.
There is a lack of understanding of how hydration may change over time in those with advanced cancer. No studies have used the paired RXc BIVA analysis to evaluate how hydration in advanced cancer changes between time points.

There is a need for further research about the risks and benefits of CAH for palliative cancer patients. However, to achieve this it is important to determine the characteristics of cancer hydration and to establish how TBW influences symptoms, physical signs and survival. It can be argued that an attempt to evaluate the benefit of CAH without knowledge of the association between TBW and symptoms may create uncertainty.

Concerning previous work, differences in the use of the terms ‘hydration’ and ‘dehydration’ may cause confusion. Many of the studies are small and of varying methodological quality. Consequently, previous studies are difficult to synthesise on account of differences in diagnostic criteria, evaluation methods, interventions and outcomes. BIA has attributes that are favourable for use in frail individuals; therefore, it has the potential to be used to improve the understanding about hydration states in advanced cancer.

7.1.2 RATIONALE FOR THE STUDY DESIGN

This study was designed with acknowledgement of the requirements of the advanced cancer patients. The study was built around a non-invasive framework to be as simple as possible for the participants. All assessment methods were selected with consideration for the welfare of the participant. The Burge and Morita assessment tools were selected in light of their simplicity; BIVA was chosen as it was non-invasive. The research team did not conduct blood tests (to facilitate study eligibility) to reduce the risk of causing distress to the participant. Instead, participants were recruited provided that blood tests were done as part of their standard clinical care. Urine tests and weight assessments were also not compulsory, but were only conducted if the participant was able to comfortably complete these assessments.
We acknowledge that there is limited data from the literature to facilitate comparison of our results; this is the first study to use BIVA to study hydration in advanced cancer. The lack of hydration core-outcome created difficulties for the sample size calculations. As no hydration core-outcomes were available from the literature we chose assessment tools with the most evidence in advanced cancer.

Several variables (physical, biochemical, symptoms, performance status and medications) were included to enable comparison between other hydration indicators through regression analysis. The observational analysis was undertaken to provide information about TBW (using regression analysis, through its association with $H^2/R$) with a provisional recruitment target of 90 patients and subsequent statistical analysis based on this number.

A primary goal of this study was to study hydration characteristics of advanced cancer patients to inform further studies using BIVA which may involve analysis at certain time points and use clinical interventions. We opportunistically conducted a longitudinal BIVA of patients receiving repeated multiple biochemical assessments to study BIVA change over time. The outcomes of first and last bio-impedance assessments were evaluated. We acknowledge that this analysis would have benefited from specified time periods for the assessments with a defined period of follow-up. However, this was beyond the scope of this project.

### 7.1.3 Theoretical Perspective for the Thesis

A post-positivist approach provided a useful framework to evaluate of the use of BIVA in the assessment of hydration in advanced cancer. Post-positivism is a contemporary empiricist view that has developed in light of criticisms surrounding logical positivism.\(^{303,304}\) Positivism assumes that objective things can be studied as fact, with the scientific methods providing the explanation and absolute truth to address the posed hypothesis. This approach was thought to be too rigid by many (including positivists themselves) who argued that the positivist explanation was too narrow to explain reality.\(^{305,306}\) Karl Popper, the famous positivist, argued that it was possible that knowledge was an illusion with the potential for an experiment or observation to demonstrate that what was previously thought to be true was
This led to the development of post-positivism, a philosophy that assumes that reality is multiple, subjective, and mentally constructed by individuals. The philosophy assumes the existence of a stable observable reality, driven by natural causes that can be measured and observed. The two approaches differ as whilst the positivist approach claims to absolute truth through the establishment of generalisation and laws, the post-positivist approach acknowledges that it is impossible for humans to truly perceive it due to their imperfect mental and sensory capacity. For Karl Popper, the disproval of theories and laws, was much more useful than verification. Therefore, the post positive approach is concerned with searching for evidence, in order, to provide proof of the existence of phenomena. Consequently, post positivism enables the researcher to critically test, and ascertain the validity of hypotheses whilst interacting with the research participants. This approach helps to develop an institutive interactive process, which leads to a greater understanding of the meaning of the outcomes which results from the subject under examination.

The principles of post-positivism have been used in research to describe a learning capacity rather than a testing one. This means that researcher recognises the common humanity that connects researchers and the research participants, rather than treating them as ‘subjects’ of an experiment. As a result, the theory has been used to acknowledge the ethical interests of research participants and prioritise their safety during involvement in research studies. This researcher-participant interaction, coupled with the acknowledgement of human complexity, emphasises good clinical practice.

This theoretical perspective provides scientific basis to establish theory, and uses repeated empirical measurements to test hypotheses. Furthermore, it acknowledges the existence of more than one reality which is experienced and influenced by the research participants. A possible example of these phenomena in this study was demonstrated by the numerical scoring system that was used to measure symptoms. It is acknowledged that symptoms reported by the patient may be influenced by various factors (related or unrelated to the item being assessed) which are difficult to quantify. Furthermore, as the subject of hydration at the end-
of-life is an emotive issue, some individuals may have beliefs or concerns based on their personal experiences. The acknowledgment of these factors will assist the interpretation of the study outcomes. Importantly, the acknowledgement that the research participant has freely agreed to take part in this research study, to assist the process of learning about reality, prioritises the duty of the research team to prevent the individual from harm.

This thesis accepted that advanced cancer is a pathological process that alters normal homeostasis. BIVA was used to measure electrical impedance to tissue interfaces. This study accepted that a change in physiological hydration was measureable by BIVA. Physiologically, fluid depletion effects the concentration of electrolytes and with subsequent modification of serum and urine biochemistry. Alteration of normal homeostasis will, in turn, affect symptoms and physical signs which will be measureable through objective and subjective assessments. In this study, several variables reportedly associated with hydration were used as independent variables whereas BIA and BIVA acted as the primary (dependent) outcome variable. Using the post-positivist framework we expected that the primary and secondary outcomes were affected by several factors. This was exemplified through the acknowledgment that hydration is an aspect of health, and the World Health Organization defines health as an 'holistic entity, involving physical, psychological, social and spiritual domains. The subject of hydration includes all aspects of this definition, which fits with the theoretical perspective of this thesis. Consequently, this thesis was written accepting that reality as perceived by the patient and researcher was important for the interpretation of the study outcomes.
SECTION 2: SUMMARY AND CRITICAL APPRAISAL OF MAIN FINDINGS

7.2.1 MAIN RESULTS OF THE STUDY

This study was completed successfully with a recruitment rate of 76.3% and no adverse events. Regression analysis demonstrated that $H^2/R$ was statistically significantly predicted by four variables. Female gender was associated with a 13.85 reduction in $H^2/R$, suggesting lower TBW ($p<.001$). Each point increase in the Burge-4 score caused a .29 reduction in $H^2/R$ ($p=.04$). Similarly, the Morita dehydration score corresponded with a 2.55 reduction in the $H^2/R$ ($p=.02$). As $H^2/R$ correlates with TBW, the findings suggest that lower TBW was associated with females and increasing intensities of the Burge-4 symptoms and Morita physical signs. Oedema was associated with a 10.94 increase in $H^2/R$, which suggests an increased TBW for these patients. The ur:cr ratio and ECOG performance status were not statistically significant in the prediction equation.

The RXc graph classified hydration status as normal in 43 (47.8%), ‘more hydrated’ in 37 (41.1%) and ‘less hydrated’ in 10 (11.1%) patients. Direct comparison between ‘less hydrated’ and ‘not less hydrated’ participants demonstrated that the ‘less hydrated’ group had significantly decreased oral fluid intake ($p=.04$). Although the ‘less hydrated’ group recorded higher values for the Burge-4 score, Morita dehydration score and biochemical variables, these did not reach statistical significance. For this cohort, the overall vector position on the RXc Z-score graph was within the normal confidence ellipse and towards the cachexia quadrant. These findings were similar to the previous cancer studies involving patients with cancers of the lung and head and neck.

Overall, median survival for the sample was 62 days [95%CI =38.76, 85.24)]. Survival was significantly shorter in patients who were ‘less hydrated’, those with pre-renal failure and those with decreasing values for $H^2/R$. These findings remained significant despite adjustment (using cox regression) for various variables.

A longitudinal analysis was conducted of the twenty-four (26.7%) participants who received multiple assessments. Evaluation of their first and last bio-impedance
measurements demonstrated that, compared to baseline, the R/H scores were higher on the final assessment (suggesting less hydration). This finding remained statistically significant in females but not in men which may suggest possible variance by gender. Change of $H^2/R$ or ur:cr ratio between the first and last assessments did not affect survival.

### 7.2.2 STRENGTHS OF THE STUDY

#### 7.2.2.1 STUDY DESIGN

The non-invasive nature of the study design was successful in the ensuring recruitment, retention and the safety of study participants. This was demonstrated by the excellent recruitment rate of 76.3% of 90 patients over ten months. This study achieved the required sample size and was able to recruit successfully from the hospice setting. Furthermore, no adverse events were reported during the course of the study and many participants agreed to receive further assessments. This bodes well for further research as it may suggest that palliative care patients want to be part of appropriately designed studies.

Our study uses BIVA, a non-invasive, reliable, validated body composition assessment tool. We used appropriate statistical methods, such as regression and survival analysis, to evaluate associations between the hydration and other factors. The assessments used in this study comprised of several clinical variables; this is an improvement on previous hydration studies which are limited in their scope. For example, this analysis included BIVA, clinical signs, patient self-reported symptoms, serum and urine biochemistry, oral fluid intake, performance status, medication review and a survival analysis. Consequently, this study provides data of various aspects of hydration states, which facilitated an in-depth analysis of several factors and identification of potential confounding factors and hypotheses for future work. Additionally, this study used BIVA to conduct a longitudinal analysis of hydration, a first in advanced cancer.

All patients were assessed in the morning by one operator using the same protocol. Consequently there was no risk of inter-observer error, although intra-observer bias
was possible. As all assessments were performed within 72 hours of serum biochemistry, which presents a quantifiable time period for the degree of association with the ur:cr ratio. This improves on previous work (about hydration in advanced cancer) which often does not report blood tests within a specified timeframe.

### 7.2.2.2 ASSESSMENT METHODS

This is the first study to use BIA and BIVA to evaluate the relationships of clinical observations, biochemistry and self-reported symptoms in advanced cancer. The BIA TBW prediction equations are inappropriate in advanced cancer due to a violation of the basic assumptions caused by cancer pathophysiology. This study did not feature prediction equations but instead used $H^2/R$ as the outcome measure. Previous cancer studies have demonstrated that $H^2/R$ has excellent correlation with TBW. $H^2/R$ was not used for the calculation or estimation of TBW volume (using subsequent prediction equations), but instead was used as a comparative index to determine relationships of the $H^2/R$ with other variables. Consequently, in this analysis, $H^2/R$ was able to evaluate relative differences in TBW although it was unable to quantify the fluid volume.

Hydration-specific signs and symptoms were evaluated (i.e. the Burge questionnaire, Morita dehydration score and oral fluid intake assessment). These tools potentially provide a standardised assessment method that can be replicated in future studies. Our analysis provided a complete assessment of the hydration status of the individual enabling statistical comparisons to be analysed.

This study involved assessments of several factors, which enabled potential confounding variables to be analysed to determine potential relationships with hydration. This included regression analyses to identify factors associated with the $H^2/R$, and an evaluation of whether specific medications influenced the Burge-4 score. This is an improvement on previous work, which often does not include assessment of potential confounding variables.
7.2.3 SUMMARY OF LIMITATIONS

7.2.3.1 METHODOLOGY

Several limitations are apparent from this analysis. As this study is observational in nature, it is not possible to determine causation between associated variables. For example, it is not possible to determine whether lower values of $H^2/R$ caused increased values of the Morita dehydration and Burge-4 score or vice versa. Further, this study had no control group, meaning that it is not possible to compare data to a non-cancer population. Consequently, the level of symptoms and physical signs that could be expected in a non-cancer group compared to this sample is unknown. Regarding BIVA, although an adult BIVA reference population was used for the RXc graph assessments, this data was based on a general medical Caucasian Italian sample which may differ in characteristics to our sample.

7.2.3.2 BIOCHEMICAL FACTORS

Concerning the biochemical tests, some patients wished to take part in the study but were unable to do so as no blood results were available. It is possible that a longer eligibility timeframe for blood tests (i.e. a cut-off of >72 hours) would have permitted greater recruitment; however, this would have increased the possibility of the blood tests being unrepresentative of the biochemical profile at the time of BIVA assessment. A tighter timeframe for recruitment (e.g. ≤24 hours) may have provided a more accurate reflection of the participant’s biochemistry at the time of BIVA assessment; however, this may have caused many to be ineligible for the study. Only four (4.4%) individuals died within seven days of study entry. Therefore, this data was not representative of patients in the last week of life. It is possible that this finding is the consequence of two methodological factors. First, only patients who had biochemical tests taken in the previous last 72 hours were included. Although this was to encourage participation it is possible that frailer patients were inadvertently excluded as a consequence. This is because dying patients are less likely to receive clinical investigations (and hence, were not eligible
for the study). Secondly, dying patients may be have been unable to provide consent, or deteriorated during the recruitment process.

7.2.3.3 BIOELECTRICAL IMPEDANCE ASSESSMENTS

A limitation of BIA and BIVA is that its interpretation is based on the assumption of constant resistivity and cross-sectional area of the human body. As highlighted earlier in chapter two, SF-BIA is based on a basic two-compartment model (fat and fat free mass) and assumes stable states of the hydration, geometry, shape, minerals and nutrients of the assessed individual. In terms of body composition, our sample was not homogenous; this was illustrated by several differences between participants (e.g. in the presence of oedema, albumin level and performance status). Consequently, although the H²/R is a simple method to compare fluid volume its interpretation was not straightforward due to the required consideration of other factors. In this study, the bio-impedance assessments were not directly compared to a reference method (e.g. deuterium dilution). Although previous validation studies (using 4-C reference models) demonstrate that H²/R is a significant predictor of TBW in cancer, the absence of a comparative reference method (in this study) meant cross-validation was not possible. Therefore, it is possible that factors on an atomic, molecular, cellular and functional level may have exerted some influence on the findings that we are unable to account for in this study.

The SF-BIA and BIVA methods are unable to distinguish between fluid compartments, anatomy or define intracellular and extracellular fluid volumes. Consequently, individuals with localised peripheral oedema may have had higher H²/R (and subsequently be placed in the more-hydrated RXc group) even if intracellular fluid volumes were lower. Therefore, this analysis was unable to determine how fluid volume compartments relate to the studied variables. Additionally, the anatomical location of oedema and its severity was not recorded. Therefore, it was not possible to determine the relationship between the location of oedema and the study variables. Clinically, this is important as the location of oedema may affect the outcomes of an individual. For example, oedema may be
peripheral in cardiac failure but more abdominally placed (ascites) in liver problems. In venous obstruction (for example, superior venae caval obstruction) the oedema is superior, whereas it is more generalised in the presence of hypoalbuminemia. These differences of oedema (according to specific diseases and conditions) may affect symptoms and survival that cannot be fully evaluated in this instance.

**7.2.3.4 TYPE OF CANCER**

This analysis involved many different cancers at various stages of illness. It is well documented that certain cancers have known associations with pathological fluid disorders. For example, abdominal ascites is prevalent with ovarian and gastric cancers,

\[ \text{\textsuperscript{317}} \] lung cancer may cause pleural effusion\[ \text{\textsuperscript{318, 319}} \] and breast cancer is associated with upper limb lymphoedema.\[ \text{\textsuperscript{320}} \] The BIVA Z-score analysis in chapter 4 demonstrated differences in the vector positions of different types of cancer. Consequently, it is possible that there was variation in body composition of participants on account of pre-existing differences related to the attributes of the specific cancer. Studies included in the comparative analysis were specific to cancer type and stage of illness. Therefore, more accuracy may have been achievable through sub-classification of cancer type and stage.

**7.2.3.5 ETHNICITY AND GENDER**

The majority of participants (n=89, 98.9%) were Caucasian; therefore, this study is only representative of this ethnicity and the data cannot be extrapolated to other ethnicities. This study included a pooled analysis of both male and females; however, some differences in BIA/BIVA were recorded on account of gender. For example, women had lower H^2/R than men, suggesting less TBW volume. This may suggest this sample was not homogenous. In light of this, our data analysis was stratified by gender; however, this reduced the sample size for the statistical analysis. The decision to include both male and females in the analysis was consistent with the methodology of previous studies.\[ \text{\textsuperscript{186, 188, 190, 200}} \] However, our data
suggests that males and females require separate BIVA analysis using the RXc method.

7.2.3.6 SAMPLE SIZE

Although this study has achieved its recruitment target, a larger sample would have provided greater opportunity to stratify data and conduct sub-analysis. Further study according to gender, age, type of cancer and oedema may have been useful in the analysis. Only ten participants were identified within the less-hydrated group; therefore, a larger sample would have helped identify the characteristics of the less-hydrated group, with comparison to the normal and more-hydrated groups. This study was not able to determine whether pulmonary oedema was present in our patients and whether this was linked to the development of secretions. Unfortunately, it was not possible to evaluate the influence of myoclonus on $H^2/R$ as this feature was only recorded one patient in the sample.

7.2.3.7 CLINICAL ASSESSMENTS

The assessment of oral intake involved subjective assessments that were conducted by various members of nursing staff. Consequently, there is the potential for discrepancy of evaluations caused by the inter-observer bias. All study assessments were conducted at earliest convenience for patients between 9am and 12pm. This variation in the timing of assessments meant that some patients received medications (including mouth care procedures) prior to the assessments whereas others did not. This may have biased the reporting of symptoms. The assessment process was conducted in order to maintain the comfort of participants (by tailoring the assessment times to the needs of the patient); however, a more standardized framework of assessment (including timing and procedural requirements concerning medications) may have been useful to reduce the potential for variation between assessments.

Patients were not fasted or required to void their bladder ahead of assessments. This was done to reduce the potential for discomfort. However, this meant that the optimum assessment conditions of BIA were not achieved. Practically, some
patients struggled to understand the VAS scoring tool. When asked to grade their symptoms using the Burge score some answered using a numerical scoring format. It is possible this highlights the familiarity of numerical scoring assessments that are commonly used by healthcare professionals during clinical assessments. Some patients perceived dry mouth and thirst to be the same and struggled to differentiate between these symptoms (a finding that is consistent with previous studies\textsuperscript{269}). Others accepted there was a difference between these variables, although they acknowledged that one would most likely affect the other. It is possible that these factors may have affected how the participants scored these items.

The Burge Dehydration Symptom Questionnaire and the Morita Dehydration Assessment score both lack validity and reliability data. These tools have been used by other researchers and were chosen for use in this study as they represented the best (and only) available hydration assessment tools in advanced cancer. However, there is no strong data to prove evidence of the validity, reliability of transferability of the tool. This study could have been improved by the incorporation of reliability testing into the design. For example, participants could have received repeat study measurements (performed by another researcher later in the same day) to compare the agreement between assessors. Furthermore, assessment tools with evidence of good reliability and validity (e.g. the Edmonton Symptom Assessment Scale\textsuperscript{321,322}) could have been used instead of (or in addition to) the chosen assessment methods. In this instance, generic symptoms could have been assessed to determine their association with hydration which may have facilitated the subsequent development of a hydration assessment tool, which could then be tested to determine its validity and reliability.

**7.2.3.8 HEIGHT AND WEIGHT ASSESSMENT**

Weight was recorded in only 28 participants. It was not possible to weigh the remainder as these individuals were not able to safely transfer. Consequently, the BMI was unobtainable in the majority of the sample. It is possible that the BMI of immobile patients was different to the rest of the sample (for example, lower BMI if
these individuals were more cachectic). In light of the expected variation of body mass in our sample, we chose a reference population featuring a BMI range of 16 – 31 kg/m². However, a narrower BMI range (relative to the expected BMI our sample) may have provided a more reliable estimation of the population.

Concerning the measurement of height measurement there were some issues with using the stadiometer in participants who were unable to stand. There were practical difficulties in manoeuvring some patients into the correct position that was required to complete the assessment.

7.2.3.9 CLINICALLY ASSISTED HYDRATION

This study is unable to provide information about the influence of CAH on BIVA or the other study outcomes. No patients received CAH in the 24 hours prior to the baseline assessments. Additionally, no information about the use (or non-use) of CAH before or after the assessments was collected. Consequently, it is not possible to determine whether CAH in the days leading up the assessments may have affected the assessments.

7.2.3.10 LONGITUDINAL ASSESSMENTS

The repeat (follow-on) assessments were not conducted at pre-defined, set time-points. This introduced variation in the timing of these assessments. Repeat assessments were done in response to blood tests. These tests were done for various clinical indications, such as a deterioration of the condition of the patient. It is possible that patients receiving follow-up assessments were different to those not receiving assessments. For example, they may represent patients who were more unwell, or experienced a change in their condition, which needed further blood tests for evaluation. Alternatively, they may represent a stable group of patients who were considered well enough to warrant routine blood tests for monitoring purposes (as opposed to those who were dying and hence, blood tests were no longer appropriate). No ongoing clinical information was collected as part of this analysis. Therefore, the use (or change in use) of therapies known to influence hydration (e.g. CAH, diuretic therapy) is unknown. Regarding the follow
up assessments no patients declined these measurements. However, some patients (although eligible to receive follow-on assessments) were not approached as they were deemed too unwell by the clinical team. Therefore, the repeat assessments were not a reflection of all participants; rather, it describes those who required additional blood tests and were considered well enough (by the clinical team) to provide consent to participate.

7.2.3.11 SURVIVAL FOLLOW UP

Due to time-related factors, the follow up period for the last patient of the study was only 3 months. Although the majority of the patients had died within this timeframe, a longer follow-up period (e.g. 12 months) may have added greater accuracy to the survival analysis.
SECTION 3: COMPARISON OF STUDY FINDINGS WITH PREVIOUS RESEARCH AND WHAT THIS STUDY ADDS TO THE EVIDENCE BASE

7.3.1 COMPARISON OF FINDINGS WITH PREVIOUS RESEARCH

7.3.1.1 H^2/R ASSOCIATIONS

The regression analysis demonstrates how H^2/R was predicted by gender, oedema, symptoms and physical signs. This is consistent with previous literature. In this study women had significantly higher R/H compared to men. This suggests that women had higher fat mass and were less hydrated compared to men. Women had a lower H^2/R, which suggests comparatively lower TBW volume. This finding is consistent with previous BIA population data\(^1\)\(^4\)\(^6\) and is consistent with accepted human physiology. Women normally have more body fat than men and therefore contain less body water than men in proportion to their weight.\(^7\)\(^0\)\(^7\)\(^1\) Oedematous participants had increased H^2/R and lower BIA vectors compared to non-oedematous participants; again, this is consistent with previous work.\(^9\)\(^5\)\(^1\)\(^5\)\(^0\)\(^2\)\(^0\)\(^4\)\(^3\)\(^2\)\(^3\)\(^4\)

The prevalence of the seven dehydration-related symptoms was similar to original data presented by Burge.\(^2\)\(^5\)\(^0\) This may suggest consistency of these symptoms in advanced cancer hospice inpatients. However, without a control group we are unable to compare these symptoms to non-cancer populations. Higher Burge-4 scores were associated lower H^2/R suggesting less TBW. This may provide evidence of the association between these symptoms and hydration. It is also consistent with the non-cancer studies that were originally done to evaluate these symptoms.\(^2\)\(^8\)\(^3\)\(^2\)\(^8\)\(^6\)\(^-\)\(^2\)\(^8\)\(^9\)

Regression analysis demonstrated that medications reportedly associated with dry mouth\(^3\)\(^2\)\(^5\) (comprising of opioids, diuretics, anticholinergics, SNRIs and SSRIs) were not predictive of the Burge-4 score. This suggests that the Burge-4 was not influenced by these medications. Regression analysis also demonstrated that the Morita dehydration score was predictive of H^2/R, a finding consistent with non-cancer studies examining the level of association that the scores’ composite variables has with dehydration.\(^2\)\(^2\)\(^5\)\(^6\)\(^2\)\(^3\)\(^1\)\(^2\)\(^5\)\(^0\) Consequently, this study provides
evidence which adds credibility to the Morita Dehydration Scores’ intended use as an assessment tool of assessing fluid status in advanced cancer patients. This analysis showed no statistically significant difference in bio-impedance measurements between patients with or without respiratory tract secretions; this suggests no significant difference in TBW. This finding is consistent with previous work which found no association between hydration level and respiratory tract secretions. However, some authors propose a link between respiratory tract secretions and pulmonary oedema.

### 7.3.1.2 COMPARISONS WITH OTHER CANCERS

Male and female bio-impedance vectors were similar to previous work involving patients affected by head, neck and lung cancer. Our sample data was within the normal 50th centile on the BIVA ‘z-score’ graph, but in a position associated with lower muscle mass. Analysis of data from the literature demonstrated that female breast cancer patients were leaner compared to other cancer populations. The reason for this difference is not clear; however, it is possible that the patients with breast cancer were healthier (possibly due to their evaluation at diagnosis as opposed to later in their illness). This is distinct from the other BIVA cancer studies which involved patients with more advanced disease.

### 7.3.1.3 LONGITUDINAL ASSESSMENTS

In other disciplines, longitudinal BIVA studies generally evaluate the effects of an intervention (for example, dialysis) through pre and post bio-impedance assessments. Some studies have also used BIVA to evaluate specific physiological situations, such as pregnancy. The results of our longitudinal analysis (using paired data for BIVA repeat assessments) demonstrated higher R/H on the final assessment compared to baseline; this may suggest that patients were less hydrated on the final assessment compared to baseline. Concerning the longitudinal assessments, the Simons et al study from 1999 is the only research which our data can be compared. Our data demonstrates that longitudinal analysis with BIVA is possible in advanced cancer and can potentially be used to
evaluate effects of an intervention, or to evaluate change in hydration in a specified time period, such as the dying phase. Comparatively, the Simons et al study found changes in $H^2/R$ and TBW occurred in both directions. It should be noted that the Simons et al study only involved patients who were part of a clinical trial evaluating the use of progestogen on food intake, a medication known to cause fluid retention. Therefore, this affects our ability to compare the results to our analysis as patients may have been more prone to fluid retention in the Simons et al study.

### 7.3.1.4 RENAL BIOCHEMISTRY

The prevalence of pre-renal failure (as defined by $ur:cr \geq 100:1$) was (41.1%, $n=37/90$); this was similar to that reported in cancer patients receiving inpatient rehabilitation (44%; $n=27/62$). Our study demonstrated a lack of association between $ur:cr$ ratio and $H^2/R$ through linear regression; however, no data for comparison was identified from the literature. Related work included a study by Valdespino-Trejo et al, in which MF-BIA was used to predict worsening renal function in patients with decompensated heart failure. This analysis demonstrated that a whole body impedance ratio (200kHz compared to 5 kHz) of $> .85$ (suggesting fluid overload) was a significant risk factor for worsening renal function ($RR=5.3$, $p=0.05$). The authors conclude that this association was likely attributable to worsening hypoalbuminaemia, through its propensity to cause decreased renal perfusion through fluid loss from the vascular space, resulting in worsening renal function and oedema.

Our work supports the findings of previous studies which find little association between renal biochemistry and the symptoms of dry mouth, thirst and respiratory tract secretions in advanced cancer patients. No statistically significant difference in the Burge-4 and Morita Dehydration scores were evident between ‘less hydrated’ and ‘not less hydrated’ participants. This may provide further evidence that biochemistry lacks sensitivity to predict hydration-related symptoms in advanced cancer patients.
7.3.1.5 SURVIVAL ANALYSIS

Regarding the survival analysis, the association of pre-renal failure with shorter survival is in-keeping with previous work in cancer patients. The cox regression survival analysis in this study was consistent with the Prognosis in Palliative care Study (PiPS) predictor models for palliative care patients. The presence of metastases and lower performance status were predictors of shorter survival, the same finding as the PiPs. Another similar finding with our study and the PiPs was the association between high urea and shorter survival. However, the ur:cr ratio was used in our analysis rather than urea alone.

Previous studies have demonstrated that haemodialysis patients classified as ‘more hydrated’ (on the RXc graph) had shorter survival compared to those normally hydrated. Similarly, survival was shorter in patients assessed with MF-BIA who were deemed to be overhydrated (relative to their ECW). Our findings differ from these studies as the individuals classified as ‘more hydrated’ lived longer than ‘normally hydrated’ and ‘less hydrated’ participants respectively. Further, shorter survival was associated with lower $H^2/R$. This may potentially highlight differences in hydration according to its relationship with disease. A possible cause for this difference is that in haemodialysis studies, ‘more-hydration’ was a consequence of adverse fluid haemostasis caused by poor renal function. This is in contrast to our cohort; where ‘more-hydration’ did not necessarily imply that patients were overhydrated (as a consequence of renal failure). It is not possible to determine the direct causal relationship of these factors. We are unable to determine the exact reason for the shorter survival suggested by lower $H^2/R$ and classification as ‘less-dehydration’. However, we can postulate that in the advanced cancer patient, the presence of ‘less hydration’ may suggest clinical deterioration or was associated with disease states with shorter survival (e.g. the anorexia cachexia syndrome). Further work is therefore necessary to determine why this difference exists.
7.3.2 CONTRIBUTION TO THE EVIDENCE BASE

This study was the first to use BIVA in advanced cancer patients to evaluate how symptoms, physical signs, and serum biochemistry are related to hydration. Concerning hydration in advanced cancer, this is the first study to report an association between clinical symptoms and hydration (measured by H²/R) through the use of an objective, validated body composition measurement tool. Our unique findings showed how H²/R was statistically significantly associated with the Burge-4 score, a composite measure of four symptoms (dry mouth, thirst, unpleasant taste and fatigue) and the Morita Dehydration Score, a composite measure of three clinical signs (dry mucous membranes, sunken eyes and dry axilla). These findings suggest that fluid volume is associated with symptoms and clinical signs. In this instance, lower fluid volumes were associated with higher scores for physical symptoms and physical signs.

This is the first study to use the RXc graph to report the characteristics of a hospice-based, mixed cancer sample. It is also the first to use the Z-score graph to evaluate differences between other cancer reference groups. Further, this research is the first to use longitudinal BIVA assessments in advanced cancer and the first to report that patients were apparently less hydrated on their final assessment compared to baseline.

This thesis adds new understanding to various aspects concerning the influence of hydration on survival in advanced cancer. The analysis of survival according to BIVA hydration classification is original. Further, the finding of the association between H²/R and survival has not previously been reported. This analysis describes how individuals with pre-renal failure experienced significantly shorter survival. Although the association between poor renal function and survival has previously been reported, this is the first study to report this using ur:cr ratio of >100:1 as a definition of renal failure in advanced cancer. Additionally, the discovery of no statistically significant difference in survival based on the change of H²/R or ur:cr ratio over time is unique.
Our study was the first to report the prevalence of less-hydration related symptoms in a UK hospice population and to compare this to the original analysis conducted by Burge in 1991. This study is the first to demonstrate the similarities of symptom prevalence across the two palliative care samples. This study had recruitment rate of 76.3% with no adverse events and consequently supports existing evidence of the safety and tolerability of BIVA. Researchers, funders and policy makers should be encouraged by our findings as this will facilitate more research in similar settings.

This analysis demonstrates that hydration in advanced cancer is complex. Research in this area requires care. Furthermore, study outcomes need to be interpreted well and communicated sensitively. This thesis used a quantitative methodology; however, this subject is complex and requires consideration of qualitative factors in order to determine how the outcomes relate to clinical practice. This analysis suggests that less hydration was associated with increased symptom intensity, higher dehydration scores and shorter survival. This may cause some to question whether CAH should have been administered; however, we are unable to comment about the role of CAH as this was not the aim of this research study.

It is important to acknowledge how language can be used to ascribe ‘value’ to certain statements about the fluid status of an individual. This can be done either intentionally or unintentionally and can add emotion to discussions (and decisions) regarding CAH. The term ‘dehydration’ has acquired a variety of subjective meanings, which differ from the original physiological definition. It can be argued that the term ‘dehydration’ now suggests inadequate hydration and hence, requires intervention (e.g. with CAH). In this study, when discussing hydration we used the phrases ‘normally hydrated’, ‘more hydrated’ and ‘less hydrated’ as we felt these were less emotive than the terms ‘over-hydrated’, ‘under-hydrated’ and ‘dehydrated’. Additionally, survival was described using the terms ‘longer’ and ‘shorter’ as these were felt to be less emotive that the comparative terms ‘better’ or ‘worse’.
7.3.3 FUTURE WORK AND UNANSWERED QUESTIONS

Researchers can use our experience to improve the methodology and conduct of future studies. Several questions arise from the outcomes of this study. Firstly, as this study describes a mixed cancer, hospice-based, Caucasian sample, it is unclear how these findings relate to other individuals of different ethnicities and those without cancer in non-hospice settings. Consequently, future studies can potentially use BIA/BIVA to evaluate hydration according to different conditions, stratified by performance status and stage of illness.

It is possible that a statistically significant difference between certain variables (Burge-4 score, ur:cr ratio, urine osmolality, ECOG and the Morita Dehydration Score) will be detected if a larger sample is studied. In this analysis ‘less hydration’ was only detected in ten patients. Although this study demonstrated an association between hydration with symptoms, physical signs and survival, it is unable to conclude whether CAH is beneficial. Future studies can use BIVA to evaluate outcomes of CAH therapy. Such studies can involve CAH as the intervention, with assessments conducted at specified time points to evaluate outcomes of BIVA (as an objective measure of hydration), physical signs, symptoms, survival and quality of life.

Our study was not representative of dying patients. Consequently, it is not possible to extrapolate our results to patients in the last hours to days of life. Future research can seek to evaluate hydration states of the dying. This approach will require innovative methodology, such as advanced consent procedures, in order, to recruit and maintain involvement of patients who are expected to lose the capacity to provide ongoing consent due to deterioration clinical condition.

This analysis shows that $H^2/R$, BIVA and pre-renal failure were predictive of survival. Consequently, there is the potential that BIA and the ur:cr ratio can be incorporated into existing assessment tools to aide prognostication in advanced cancer patients. Additionally, BIVA could be used to evaluate non-hydration factors in the palliative cohort (for example, to assess muscle mass in the evaluation of cachexia). Furthermore, BIVA could be used to evaluate body composition changes in
response to clinical treatments such as radiotherapy and chemotherapy, in order, to predict outcome. Future studies can use H²/R and BIVA to evaluate survival for various diagnoses at different stages of disease, particularly the last hours to days of life. Additionally, the marker of phase angle (which has been found to be associated with survival in previous studies) can be further evaluated to assess to test its usefulness and its relationship with hydration.

7.3.4 CONCLUDING REMARKS

This study is the first to demonstrate how fluid status is associated with symptoms, survival and physical signs in advanced cancer. This sheds new light on the subject of hydration in palliative care. Our data suggest that a good level of recruitment to studies involving palliative patients is possible. This is noteworthy, as patients in specialist palliative care units are more likely to have more advanced disease and symptom burden compared to those within general medical and oncology units. Researchers, funders and policy makers should be encouraged by our findings as patient participation in research will help to identify and address patient-centred priorities at the end of life. This thesis demonstrates that the subject of hydration in advanced cancer is complex, under-researched and methodologically challenging. Rather than a simple question of whether CAH should be administered or not, it represents a multi-faceted issue that requires a careful decision making. Several factors need to be considered, which include diagnosis, stage of disease, gender, ethnicity, symptoms, use of medications, performance status, quality of life, oedema and the potential risks and benefits of CAH.

Further work is essential to learn more about hydration according to different types of cancer, at specified disease stages and whether medical interventions are of benefit in these scenarios. Consequently, this study provides the first step of journey which will hopefully improve the care of advanced cancer patients throughout the world.
Appendix 1 - Mathematical Formulas

Formulas used in the development of the BIVA method are presented in this section.

**Equation 1: Development of the impedance index formula (see introduction 1.3.4 Use of BIA to predict fluid volumes)**

The impedance \( Z \) of a human body is a function of the specific electrical resistivity \( \rho \, (\Omega \cdot \text{cm}^2) \) of the adipidic tissue (a good conductor of electrical current) and is obtained by its section \( A \, (\text{cm}^2) \) and length \( L \, (\text{cm}) \):

\[
Z = \rho \frac{L}{A}^{335}
\]

Considering the lean body mass as a cylinder, the equation can be rewritten by multiplying by \( L/L \):

\[
Z = \rho \frac{L^2}{A \cdot L}^{93}
\]

Replacement of \( A(L) \) with volume \( V \, (\text{cm}^3) \) and adapting the equation e will obtain:

\[
V = \rho \frac{L^2}{Z}^{119}
\]

Consequently, the use of an alternating current and cylindrical electrical conductor will allow:

\[
V = \rho \frac{L^2}{R}^{336}
\]

Therefore, if \( \rho \) is constant, \( L^2/R \) is directly proportional to the volume of the lean body mass. The fundamental laws of the impedance measurement are in Nyboer J’s book.\(^{92}\) In the human subject, height is used as a measure of the conductor length. Therefore the final equation is:

Volume = height\(^2\)/impedance.\(^{92}\)

Parameters of tolerance ellipses of bivariate Z-scores (RXc-score graph) can be calculated accordingly, using equations 2 and 3.\(^{144}\)
Equations 2 and 3: Formulas for the calculation of the bio-impedance confidence and tolerance ellipses

The following section has been adapted (with permission) from Piccoli A, Pastori: BIVA software.\textsuperscript{101}

Geometrical parameters for drawing the RXc Graph and the RXc-score Graph

Confidence and tolerance intervals can be calculated for the bivariate normal distribution.\textsuperscript{148} 337-340 A simple linear correlation analysis can be used for calculation following appropriate modification of the equations.\textsuperscript{142} 144

Given \( n \) pairs of observations \( x \) and \( y \), with standard deviation \( s_x \) and \( s_y \), and correlation coefficient \( r \), for a fixed \( \alpha \) probability level, the Snedecor’s \( F_\alpha \) value is taken with 2 and \( n-2 \) degrees of freedom.

RXc Graph

The RXc graph semi-axes (\( L_1 \) and \( L_2 \)) and the slopes (\( b_1 \) and \( b_2 = -1/b_1 \)), of the axes of the 100(1-\( \alpha \))% confidence and tolerance ellipses (e.g. \( \alpha = 0.05, 0.25, \) and 0.50 for the 95th, 75th, and 50th percentile, respectively) can be calculated using the equations 2a and 3a, respectively.

RXc-score graph

The parameters of tolerance ellipses of bivariate Z-scores (RXc Z-score graph) can be calculated accordingly, using equations 2b and 3b.\textsuperscript{144}

Equation 2 a (See 1.4.3: The RXc graph method in clinical bio-impedance analysis)

\[
L_1, L_2 = \sqrt{K} \sqrt{(n - 1)(s_{x^2} + x_{y^2})} \pm \sqrt{[(n - 1)(s_{x^2} + s_{y^2})]^2 - 4(n - 1)^2(1 - r^2)s_{x^2} s_{y^2}}
\]
Equation 2 b

\[ L_1, L_2 = \sqrt{K} \cdot \sqrt{2 (n - 1) \pm 2 r (n - 1)} \]

Where

- \( K = F/n \cdot (n-2) \) for confidence ellipses
- \( K = F \cdot (n+1)/n \cdot (n-2) \) for tolerance ellipses

Equation 3 a

\[ b_1, b_2 = \left( b, \frac{1}{b} \right) = \left( b_y^2 - b_x^2 \right) / 2 rs \pm \sqrt{1 + \left[ \left( s_y^2 - s_x^2 \right) / 2 rs \right]^2} \]

Equation 3b

\[ b_1, b_2 = \pm 1 \]
## Appendix 2: Details of studies included in the literature review

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Design</th>
<th>Participants</th>
<th>Exclusions</th>
<th>Dehydration definition</th>
<th>Outcome measure</th>
<th>Methods</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Morita et al 2005[^22^] | To explore systematically the associations between hydration volume and dehydration and fluid retention symptoms in the last 3 weeks of life in terminally ill patients with abdominal malignancies. | Multicentre, prospective, observational study | n=226                                                                         | n=272                                                                       | Degree of dehydration defined on basis of three physical findings.                     | 1. Ad Hoc dehydration score (0-5)  
2. The peripheral oedema score (0-21)  
3. Pleural effusion score (0-2)  
4. Ascites score (0-2)  
5. Delirium (evaluated by the Memorial Delirium Assessment Scale) | Analysis of data collected: Patients classified into 2 groups; the hydration group (n=59) who received ≥1 L or more of artificial hydration per day both 1 and 3 weeks before death, and the non-hydration group (n=167) who did not. | Percentage of patients with deterioration in dehydration score in final 3 weeks of life significantly higher in non-hydration group compared to hydration group (35% versus 14%, p=0.002). Fluid retention symptoms increased significantly in hydration group compared to non-hydration group: oedema (44 versus 29%, p=0.039) ascites (29% versus 8.4%, p=0.001), pleural effusion (15% versus 5.4%, p=0.016). No significant difference in degree of bronchial secretion, hyperactive delirium, communication capacity, agitation, myoclonus or bedsores. |
Morita et al 2006

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Study Design</th>
<th>n</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Degree of dehydration defined on basis of three physical findings</th>
<th>Secondary analysis of data collected:</th>
</tr>
</thead>
<tbody>
<tr>
<td>To explore the association between (1) hydration volume and laboratory findings and (2) calculated fluid balance and the changes in clinical signs of dehydration and fluid retention during the last 3 weeks of life in terminally ill cancer patients.</td>
<td>Multicentre, prospective, observational study</td>
<td>125</td>
<td>Age ≥ 20</td>
<td>Life expectancy ≤ 3 months</td>
<td>Incurable malignancy of lung or abdominal origin (excluding hepatic malignancies).</td>
<td>1. Ad Hoc dehydration score (0-5)</td>
<td>Laboratory data; Clinical assessment data; Fluid balance; Oral intake.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male/female = 61/64</td>
<td></td>
<td>Mean age = 67</td>
<td>Number not given</td>
<td>2. The peripheral oedema score (0-21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>liver cirrhosis, renal failure, nephritis syndrome, protein-losing enteropathy, intra-abdominal shunt for ascites, hypercalcaemia, endocrine disorders, and vital organ complications unrelated to underlying malignancies; surgical, radiological, or oncological treatments in the 3 weeks prior to study inclusion; existing communication difficulty; and the use of artificial enteral nutrition.</td>
<td>3. Pleural effusion score (0-2)</td>
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<td></td>
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<td></td>
<td></td>
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<td>4. Ascites score (0-2)</td>
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</tbody>
</table>
| **Bruera et al 2005** | To determine the effect of clinically assisted hydration on overall symptom control in terminally ill cancer patients with dehydration. | Randomised, controlled, double-blind trial. | n= 51  
NB: sample size calculation 54 per group (i.e. total n=108)  
- A palliative diagnosis of advanced cancer with no further treatment planned.  
- Oral intake ≤ 1000 mL/day;  
- decreased skin turgor ≥ 2 seconds.  
- One or more of: dry mouth; thirst; decreased volume of urine output; a darker colour of urine than usual  
- Laboratory values consistent with dehydration obtained within 24 hours of admission to the study.  
- Age ≥16  
- Able to tolerate subcutaneous or intravenous fluids.  
  Demographics not given  
  Target symptoms (hallucinations, myoclonus, fatigue, and sedation) assessed with 0-10 numeric rating scale.  
  Mini Mental State Examination (MMSE). | n= 13  
patient’s refusal to participate; the presence of severe dehydration, defined as a decreased systolic resting blood pressure of 30 mmHg or lower from the patient’s baseline value; low perfusion of the limbs; no urine output for 12 hours or longer; a decreased level of consciousness; or evidence of severe renal failure or bilateral hydronephrosis.  
Oral intake ≤ 1000 mL/day;  
- decreased skin turgor ≥ 2 seconds.  
- one or more of: dry mouth; thirst; decreased volume of urine output; a darker colour of urine than usual laboratory values consistent with dehydration, such as an elevated blood urea nitrogen to creatinine (BUN/Cr) ratio of ≥20:1.  
Target symptoms (hallucinations, myoclonus, fatigue, and sedation) assessed with 0-10 numeric rating scale. | Target symptoms (hallucinations, myoclonus, fatigue, and sedation) assessed with 0-10 numeric rating scale.  
Mini Mental State Examination (MMSE). | Patients were randomly assigned to receive either 1,000 mL (treatment group) or 100 mL (placebo) normal saline administered over 4 hours for 2 days.  
Patients evaluated for target symptoms global well-being, and overall benefit. | The administration of artificial fluids improved sedation and myoclonus in the intervention group. |
| **Bruera et al 2013** | To determine whether parenteral hydration was superior to placebo | Randomised, placebo-controlled,  
NB: Sample size | n=129  
- Declined to participate  
- Defined by decreased skin turgor in  
  Defined by decreased skin turgor in  
  Defined by decreased skin turgor in | Target symptoms (hallucinations, myoclonus, fatigue, delirium and | Patients were randomly assigned to  
  Defined by decreased skin turgor in | Hydration at 1L per day did not improve symptoms, quality of |
in improving symptoms associated with dehydration, delayed the onset and severity of delirium, and had an effect on quality of life (QoL) and survival in patients with advanced cancer receiving hospice care.

**Double-blind, multicentre trial.**

- Diagnosis of advanced cancer
- Age ≥ 18 years
- An admission to Hospice
- A reduced oral intake of fluids with evidence of dehydration (see dehydration definition)
- A life expectancy ≥1 Week
- Availability of a primary caregiver
- A Memorial Delirium Assessment Scale (MDAS) score less than 13
- Able to give written informed consent
- Lives within 60 miles of The University of Texas MD Anderson Cancer Center.

**Calculation was 75 per group (i.e. total n=150)**

- Did not meet inclusion criteria (n=387)
- Delirium/actively dying (n=110)
- No dehydration (n=26)
- Non-English speaking (n=25)
- Brain metastases (n=22)
- Other (n=204)
- Died (n=154)
- Unable to contact (n=30)

**Subclavicular region (>2 seconds) and a score of ≥2 of 5 in the clinical dehydration assessment**

**Sedation assessment with 0-10 numeric rating scale.**

- Edmonton Symptom Assessment Scale
- Unified Myoclonus Rating Scale (UMRS)
- Memorial Delirium Assessment Scale (MDAS)
- Richmond Agitation Sedition Scale (RASS)
- Nursing Delirium Screening Scale (NuDESC)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

**Global symptom evaluation was used to estimate minimal importance difference in target symptoms pre and post treatment.**

---

**Guo et al 2007**

To determine the prevalence of pre-renal azotaemia in a cancer rehabilitation patient population.

To evaluate the relationship of pre-renal azotaemia to rehabilitation outcome.

**Retrospective chart review**

<table>
<thead>
<tr>
<th>n=62 Cancer patients admitted to the acute inpatient rehabilitation unit: Demographics not given.</th>
<th>n=8 Patients considered to have renal insufficiency</th>
<th>BUN/Cr ratio ≥ 20 (pre-renal azotaemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pre-renal azotaemia prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Length of rehabilitation stay of pre-renal azotaemia group compared to non pre-renal azotaemia group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Discharge destiny of pre-renal azotaemia group</td>
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</tbody>
</table>

Patients classified into 2 groups: The pre-renal azotaemia group (n=27) and the non pre-renal azotaemia group (n=35).

Pre-renal azotaemia prevalence = 44% (n=27/62)

No significant association between pre-renal azotaemia on length of rehabilitation stay or discharge destiny.
specifically length of stay and discharge destiny in these patients.

<p>| Waller et al 1994&lt;sup&gt;609&lt;/sup&gt; | Are cancer patients dehydrated when close to death? Does the provision of intravenous fluids influence the state of hydration of such patients or their level of consciousness? | Cross-sectional | n= 68 Hospice inpatients: - Terminal cancer - Laboratory tests done within 48 hours of death (patients selected after death) Demographics not given | Number and details not given | Elevated sodium, specific cut-off was not defined. Differences between urea, sodium, serum osmolality, urine osmolality, urine/serum osmolality ratio, blood urea nitrogen (BUN)/creatinine ratio. Alertness scale: 1. Fully conscious 2. Responsive to visual or vocal stimuli 3. Responsive to only painful stimuli 4. Comatose The Early Warning Score (EWS) is validated for the identification of medical patients at risk general deterioration. | Comparison of biochemical measurements and alertness scale measurements between groups. 87% [n= 59/68] of patients classified as dehydrated. State of consciousness correlated inversely with serum sodium and urine osmolality. Patients receiving intravenous fluids were not better hydrated than those without IV therapy. State of consciousness was not improved for those hydrated compare to those without IV therapy. |
| Burge et al 1993&lt;sup&gt;610&lt;/sup&gt; | To determine the severity and distribution of symptoms associated with dehydration in inpatient palliative care patients. | Cross sectional survey | n= 52 Palliative care unit (PCU) patients: - Age ≥18 - Advanced cancer - Prognosis ≤6 weeks - Ability to speak English or French | n= 71 - Confusion (n=20) - Weak (n= 7) - Drowsy/coma (n=13) - Language (n=7) - Died (n=5) - Refused (n=5) - Aphasia (n=2) | Dehydration not defined | Visual analogue score (VAS) for following symptoms: - Thirst - Pain - Dry mouth - Nausea - Bad taste - Fatigue - Pleasure to drink | Cross sectional survey of palliative care inpatients across to hospitals. Associations between | No association between severity of symptoms and fluid intake. No association between biochemical measures and thirst. Fatigue, dry mouth and... |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective Measures</th>
<th>Methods</th>
<th>Outcome Measures</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerchietti et al 2000</td>
<td>Association between these objective measures of dehydration</td>
<td>Randomised controlled trial, n=42</td>
<td>Dehydration diagnosed on physical examination (with or without renal failure)</td>
<td>Both groups showed significant and equal improvements in relief of thirst and nausea at 24 hours, but this improvement was only maintained in the hydration group at 48 hours. Delirium did not improve significantly in either group.</td>
</tr>
<tr>
<td>Ellershaw et al 1995</td>
<td>To assess the usefulness of hypodermoclysis hydration in the relief of thirst, chronic nausea and delirium</td>
<td>Prospective cohort, n=82</td>
<td>Dehydration based on presence of one or more of the following: - Thirst - Chronic nausea - Delirium - MMSE</td>
<td>No statistically significant relationship between respiratory tract secretions, dry mouth and thirst and the level of hydration.</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>n</td>
<td>Inclusion Criteria</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Morita et al 2001</td>
<td>To identify the association between sensation of thirst in hospice inpatients and various medical factors, especially dehydration.</td>
<td>Cross-sectional study</td>
<td>n=88</td>
<td>Palliative care inpatients: - Age ≥18 or older - Diagnosis of incurable advanced cancer - Physicians’ estimate of 6 months life expectancy or less.</td>
</tr>
<tr>
<td>Galanakis et al</td>
<td>To estimate the extent to which hydration and Retrospective analysis of</td>
<td>n=1125 Patients with</td>
<td>n=1390</td>
<td>Dehydration not defined</td>
</tr>
<tr>
<td>Year</td>
<td>Study Details</td>
<td>Patient Characteristics</td>
<td>Methods</td>
<td>Outcomes</td>
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<tr>
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<tr>
<td>2010</td>
<td>Related risk factors influence the course of delirium over time.</td>
<td>Advanced cancer surviving at least 3 days, receiving care palliative care at centres in Quebec and Ontario as part of a clinical trial for the prevention of delirium.</td>
<td>Data unavailable</td>
<td>Details of measures unavailable.</td>
</tr>
<tr>
<td>2012</td>
<td>To clarify the longitudinal changes in patient reported global quality of life (QoL), observational discomfort, symptoms and fluid retention signs in patients with advanced cancer receiving guideline-based parenteral hydration therapy.</td>
<td>n=161 - &gt;20 years - Incurable abdominal malignancy - Severely reduced oral intake (&lt; 100 kcal/day and 100 mL/day); - Available for follow-up</td>
<td>- Hepatic, prostate, or oesophageal malignancy - Renal (creatinine&gt; 2 mg/dL), - Heart (NYHA classification &gt;II), or liver failure (total bilirubin &gt; 2 mg/dL) unrelated to malignancy - Liver cirrhosis, nephrotic syndrome, or protein-losing enteropathy of any aetiology - Intra-abdominal shunt for ascites;</td>
<td>Dehydration not defined</td>
</tr>
</tbody>
</table>
| Nakajima et al 2013\(^{257}\) | To explore the influences of hydration volume toward the symptoms during the last 3 weeks of life in these patients. | Prospective, observational study | n=75  
- Age > 20 years  
- Life expectancy estimated by a physician to be < 3 months  
- Incurable malignancy of abdominal origin. | Number not given.  
- Liver cirrhosis  
- Renal failure  
- Nephrotic syndrome  
- Protein-losing enteropathy  
- Intra-abdominal shunt for ascites  
- Hypercalcaemia  
- Adrenalopathy  
- Thyroid diseases  
- Other complications of the circulatory, respiratory, hepatic, or renal system unrelated to underlying malignancies  
- Surgical, radiological, or oncological treatments with the primary intent of tumour reduction in the three weeks prior to study inclusion  
- Communication difficulty | Degree of dehydration defined on basis of three physical findings.  
1. Dehydration score\(^{35}\)  
2. The peripheral oedema score  
3. Ascites and pleural effusion score  
4. Bronchial secretion  
5. Delirium (evaluated by the Memorial Delirium Assessment Scale) | Analysis of data collected:  
Patients classified into 2 groups; the hydration group (n=32) who received ≥1 L or more of artificial hydration per day both 1 and 3 weeks before death, and the non-hydration group (n= 43) who did not. | The percentages of patients with deterioration in dehydration score in the last 3 weeks were significantly higher in the non-hydration group than in the hydration group (35% versus 13%; p=0.027).  
Significantly higher fluid retention symptoms reported in the hydration group compared to the non-hydration group:  
oedema (57% versus 33%, p=0.040), ascites (34% vs. 14%, p=0.037) and bronchial secretion (44% vs. 19%, p=0.036).  
No significant differences in the degree of pleural effusion and delirium. |
<p>| <strong>Musgrave et al 1995</strong>&lt;sup&gt;252&lt;/sup&gt; | To evaluate the effects of intravenous fluids in a group of dying patients. | <strong>Cross-sectional study</strong> | <em>n</em> = 19&lt;br&gt; - Inpatients on adult oncology unit:&lt;br&gt;  - Terminally ill&lt;br&gt;  - Receiving IV fluids&lt;br&gt;  - Prognosis of ≤10 days&lt;br&gt; Demographics not given | *<em>n</em> = 19&lt;br&gt; - Survival &gt; 10 days&lt;br&gt; (n=5)&lt;br&gt; - Died without IV (n=1)&lt;br&gt; - Transferred (n=2)&lt;br&gt; - (Semi)unconscious (n=11) | <strong>Dehydration not defined</strong>&lt;br&gt; Structured questionnaire developed by the researchers.&lt;br&gt; Questionnaire was reviewed for content validity by an oncologist, two specialists in oncology nursing and two statisticians.&lt;br&gt; Patients asked to complete a questionnaire recording severity of thirst. Serum biochemistry and fluid intake and output volumes recorded. Comparisons made between variables. | 95% (<em>n</em> = 18/19) of patients reported thirst.&lt;br&gt; No association between level of thirst with the amount of IV fluids received, blood urea nitrogen, sodium levels.&lt;br&gt; Little association between fluid retention signs and volume of fluid received. |
| <strong>Davis et al 2009</strong>&lt;sup&gt;280&lt;/sup&gt; | To determine whether bioelectrical impedance analysis (BIA) correlates with hydration changes during clinically assisted hydration and to determine if these changes were of prognostic importance. | <strong>Prospective observational study</strong> | <em>n</em> = 50&lt;br&gt; - Inpatient palliative care unit:&lt;br&gt;  - Active cancer&lt;br&gt;  - Undergoing continuous hydration&lt;br&gt;  - Able to give consent&lt;br&gt; Mean age = 63&lt;br&gt; Male/female = 30/20 | <em>n</em> = 29&lt;br&gt; - Delirious&lt;br&gt; - Actively dying&lt;br&gt; - Unable to communicate&lt;br&gt; - Deferred participation&lt;br&gt; - Patients with defibrillators | <strong>Dehydration not defined</strong>&lt;br&gt; Phase angle.&lt;br&gt; Patients underwent BIA measurements for 3 consecutive days. Laboratory studies, patient weight and vital signs recorded. Patient survival calculated. | Higher phase angle before hydration predicts longer survival.&lt;br&gt; Increase in phase angles during hydration predicted poorer survival and pre-existing intracellular dehydration, cachexia or poor membrane function. |
| <strong>Crawford et al 2009</strong>&lt;sup&gt;289&lt;/sup&gt; | To investigate whether bioimpedance spectroscopy (BIS) has the potential to improve prognostication in an outpatient clinic for patients with cancer receiving palliative care. | <strong>Observational</strong>&lt;br&gt; <em>n</em> = 84&lt;br&gt; - Outpatient oncology and palliative care clinics:&lt;br&gt;  - Advanced cancer&lt;br&gt;  - Fluency in English&lt;br&gt;  - Age ≥18&lt;br&gt;  - Judged by their primary medial specialist to be in the palliative phase of | <em>n</em> = 19&lt;br&gt; - Declined participation (n=4)&lt;br&gt; - Physical decline (n=15) | <strong>Dehydration not defined</strong>&lt;br&gt; BIS measures and survival time.&lt;br&gt; Survival time and BIS measurements of basal metabolic rate and measurement 11 body composition parameters (extracellular fluid (ECF)), | Metabolic rate and accumulation of body fluid are indicators of poor prognosis in palliative cancer patients. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fritzson et al 2013</td>
<td>Association between parenteral fluids and symptoms in hospital end-of-life care: an observational study of 280 patients.</td>
<td>n=251 - Patients who were reported to Swedish Register of Palliative Care to have died expectedly in a hospital in the Västerbotten county (Sweden) between 1 January 2011 and 30 June 2012.</td>
<td>To investigate whether dying patients receiving CAH suffer from more or less symptoms than patients who do not receive CAH.</td>
<td>Dehydration not defined.</td>
</tr>
<tr>
<td>Simons et al 1995</td>
<td>The use of bioelectrical impedance analysis to predict total body water in patients with cancer cachexia</td>
<td>n=41 - Ambulatory - Cancer diagnosis</td>
<td>To investigate the applicability of BIA to determine TBW by using deuterium dilution as a reference method in end-stage cancer</td>
<td>Dehydration not defined.</td>
</tr>
</tbody>
</table>

**Documented presence of dyspnoea, respiratory secretions, anxiety, nausea and confusion in the last 24 hours of life.**

**Patients classified into two groups using stratified random sampling:**
(i) CAH group (n=140)
(ii) non-CAH group (n=140).

Patients matched by age, sex and disease.

Higher dyspnoea prevalence in the CAH group vs. non-CAH group (51% vs 22% last 24 h, p<0.0001; 70% vs 45% last 7 days, p<0.001). Increasing prevalence of dyspnoea was associated with larger CAH volumes. No clinically significant differences in anxiety, nausea or confusion were found.

**Correlations between H2/R, Δ-TBWdeu and TBW as estimated by prediction equations were**

H2/R was a strong predictor of Δ-TBWdeu in both normal-weight patients (r² = 0.85, p<.0001) and underweight patients (r² = 0.86, p<.0001). SF-BIA overestimates TBW in underweight patients when prediction formulas are used that have been developed in normal-weight subjects.
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simons et al 1999</td>
<td>Bioelectrical impedance analysis to assess changes in total body water in patients with cancer.</td>
<td>To compare changes in $H^2/R$ with changes in $\Delta$-TBWdeu in cancer patients over 12 weeks.</td>
<td>n=33 - Advanced-stage cancer patients who participated in a randomized placebo-controlled trial investigating the effects of a synthetic progestogen on food intake and body composition. n=21 - No repeat assessment (n=16) - Death or physical deterioration (n=6) - Side effects (n=4) - Refusal to continue (n=2) - Protocol violation (n=2) - Mechanical gastric obstruction (n=1) - Peritonitis (n=1) Dehydration not defined.</td>
<td>Changes in TBWdeu occurred in both directions (mean +0.2 +/- 1.6 L, range -3.3 to +3.1 L). Changes were significantly predicted by changes in $H^2/R$ ($r^2 =0.43$, $P &lt;.0001$, SEE 1.22 L), although precision was poor (residual SD = 1.2 L).</td>
</tr>
</tbody>
</table>
Appendix 3: Study advertisement poster

HYDRATION IN PALLIATIVE CANCER PATIENTS: THE TESTING OF A NEW ASSESSMENT METHOD

Marie Curie Hospice Liverpool is currently participating in a study to improve the knowledge of hydration in people with advanced cancer

Inclusion criteria

- Admitted to the Marie Curie Hospice Liverpool.
- Over 18 years of age.
- Known diagnosis of cancer (proven by histology or radiological imaging).
- No further curative treatment possible.
- Able to understand the study protocol in English or through the use of communication aides or interpreter services.

Exclusion criteria

- Patients with implantable defibrillator devices or pacemakers.
- Patients unable to provide fully informed consent.

IF YOU BECOME AWARE OF PATIENTS WHO YOU BELIEVE FIT THE ABOVE CRITERIA AND MAY BE WILLING TO PARTICIPATE IN THE STUDY PLEASE CONTACT:

Dr Ami Nwosu

Email: anwosu@liv.ac.uk
Appendix 4: Healthcare professionals’ factsheet

Hydration in advanced cancer patients: the testing of a new assessment method – RESEARCH STUDY FACTSHEET

What is the purpose of the study?
The aim of this study is to improve the knowledge of hydration in people with advanced cancer. Currently there is limited scientific knowledge of hydration states in cancer.

Why is this study needed?
There is little evidence or guidance around the role of clinically assisted hydration (CAH) at the end-of-life. Little is known about the potential benefits of CAH; however, use of CAH may potentially be harmful. This uncertainty can cause great distress to patients, family and staff.

What does this study involve?
Consenting adult cancer patients in the hospice will have their hydration status evaluated through the use of a machine called a ‘body analyser’. The machine is quick, simple to use, safe, portable. It is similar to technology currently used in gyms. The whole process will be similar to having an electrocardiogram (ECG) done.

What will happen to patients taking part in the study?
1. Interview – to obtain details of participant’s medical history
2. Hydration symptom questionnaire – Visual analogue scale for seven symptoms.
3. Clinical examination – limited examination of eyes, armpit and mouth.
4. Body analyser hydration assessment
5. Urine tests – Where possible, a urine sample will be collected.
6. Height and weight - will be recorded; height can be done lying down in the individual is unable to stand. If able, the participant will be weighed using a weighing scale chair.

What will I have to do?
Simply let patients know that there is a research study taking place in the hospice and whether they object to a researcher speaking to them about this further.

Will this affect patient care?
Patient care will NOT be affected. Information from assessments will not be available at the bedside and will be anonymised for subsequent data analysis. The hydration analyser will NOT be able to provide information about their hydration at the bedside. Patients are free to withdraw from the study at any time.

How will this study help patients?
This study will act as the first step in improving the knowledge of hydration states in advanced cancer, to facilitate future work, which may include studies using a fluid ‘drip’ to test its use in the treatment of symptoms. Knowledge gained from this research will support further work, to improve the management of hydration states in advanced cancer, to ultimately improve patient care.

How can I find out more information?
Dr Ami Nwosu, Academic Research Fellow
Ami.Nwosu@mariecurie.org.uk

This research is supported by a monetary grant by the Friends of the University of Liverpool.
Appendix 5: Letter to General Practitioner

Version 1; July 2012

Patient details:

Date: XX-XX-XX

Dear Doctor,

This letter is to inform you that the above patient is currently enrolled on the ‘Hydration in palliative cancer patients: the evaluation of a novel assessment technique’ study. This study is taking place at the Marie Curie Palliative Care Institute Liverpool between August 2012 and July 2013. This study will not affect their day-to-day treatment and will not affect their medication therapy. Therefore, this patient’s management of should not be influenced or altered by their participation in this study.

If you require any further information please do not hesitate to contact me.

Yours sincerely,

Dr Amara Nwosu

Academic Research Fellow in Palliative Medicine
APPENDIX 6: Consent process

MARIE CURIE HOSPICE LIVERPOOL
Generic information available for patients, relatives, staff introducing the research study and offering contact details for further information for those interested

New admissions to hospice?

Clinical team informs patient about the research project. Provides information sheet 1 (APPENDIX 5) if necessary.

Clinical team gain permission from patient to allow approach from the research team, in order to provide them with further study information

Researcher makes initial approach to patient to introduce the study and will provide information sheets. The researcher will explain they will return 24 hours later to further discuss the study.

Patient agrees to enter study

Yes

Sign Consent form

Yes

Screening questions

Case note review

Patient needs more time/information before making decision

The researcher will arrange another meeting at a convenient date and time for the patient

Eligible for entry into study?

Yes

Assessment schedule

No

Patient does not want to participate in study

No further action – unless requested by patient at a later date

No further action unless patient becomes eligible at a later date

Patient becomes eligible for study entry
Appendix 7: Participant information sheet - Part 1

Title of Project: Hydration in palliative cancer patients: the testing of a new assessment method

Contact for further information:
Dr Amara Nwosu
Research co-ordinator
Marie Curie Palliative Care Institute Liverpool (MCPCIL)
University of Liverpool, Cancer Research Centre
200 London Rd
Liverpool, L3 9TA
Tel: 0151 794 8972
Email: ami.nwosu@mariecurie.org.uk

Introduction

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it will involve for you. One of our team will go through the information sheet with you and answer any questions you have. Ask us if there is anything that is not clear.

What is the purpose of the study?

The aim of this study is to improve the understanding of how advanced cancer affects hydration. Hydration levels may be different in people with cancer, when compared, to people who do not have cancer; however, little is known about this. Sometimes people may receive fluids by ‘a drip’ for various reasons, including dehydration. Fluids can be given by a small needle, into a vein or alternatively, to the tissue beneath the skin. However, research is limited, and we currently know little about when fluids may be helpful or harmful.

We plan to measure the hydration levels in people affected by cancer. We will do this by using a simple, safe, hand-held machine called a ‘body analyser’. The machine is quick and simple to use and is similar to technology currently used in gyms. The whole process will be similar to have an electrocardiogram (ECG) done. The hope is in the future, doctors will be able to make better decisions when deciding to start a fluid drip in people with cancer.
Why have I been invited?

We are offering all people admitted to the hospice from October 2012 the opportunity to take part in our study. If you have cancer we are interested in learning more about how your body regulates your water content.

Do I have to take part?

It is up to you to decide to join the study. We will explain the study and go through this information sheet with you. If you agree to take part, we will then ask you to sign a consent form once you have had time to read the information. Your participation in the study will be confidential. The clinical care you receive in the hospice will not be affected by you decide to participate or not.

What will happen to me if I take part?

1. Interview – we will ask a few questions about your health and will review your medical records.

2. Hydration symptom questionnaire – we will ask you to mark one point on a line to indicate the average intensity of seven symptoms over the past 24 hours.

3. Clinical examination – a doctor will visually inspect your eyes and check your mouth and armpits for moisture.

4. Hydration assessment – we will use the body analyser to measure your hydration.

5. Blood and urine tests – To participate you will need to have had a blood test measuring your kidney function, taken in the past 3 days, as part of your clinical care. We may also ask you to provide a urine sample

The whole process listed above should take 30 minutes. You will be invited to have the above repeated if you have any more blood tests done (as part of your clinical care) whilst you are in the hospice.

What will I have to do?

To take part in the study you should further discuss with Dr Amara Nwosu, the research coordinator. You will be provided with the additional information in part 2 of the information sheet for you to read. If you agree to participate you will be asked to sign a consent form.
Appendix 8: Participant information sheet – Part 2

What will happen to me if I take part?

1. Interview

If you take part a member of the research team will initially ask you some questions about your medical history. This will include details of your age, current (and previous medical) conditions and any problems you may have experienced in the past week. We will look at your clinical records to note the medications you are taking. We will also record the amount of fluid you have either drank, or received through a drip or a feeding tube (if you have one).

2. Hydration symptom questionnaire

If you agree to take part in the study we will ask you to complete a short written questionnaire. You will be asked to mark one point on the line to indicate the average intensity of seven symptoms over the past 24 hours.

3. Clinical examination

The researcher will complete a brief clinical examination to look at your eyes, mouth and armpits to assess the dryness of these areas. We will measure your height may record your weight.

4. Hydration assessment

We will use a machine called a body analyser to assess your water content. This is a small machine with three leads which will be placed on your skin. The leads will have a small sticky pad which will attach lightly to your skin, it will not hurt you. Leads will be placed on your right hand and right foot, once activated the machine will then collect the information. Similar technology is currently used in gyms. The whole process is similar to having an electrocardiogram (ECG) done. Information from the assessments will be analysed at the end of the study to learn about the hydration status of participants. It is not possible to give you results at the bedside. The testing process is completely safe and pain free.

5. Blood and urine tests

The results of blood and urine results you have had taken whilst in the hospice will also be recorded. In order to learn more about your water content, we may add additional tests to the blood sample you have already had taken. We may also ask
you to provide a urine sample if this has not been done during your stay in the hospice.

The whole process listed above should take 30 minutes. You will be invited to have these steps repeated if you have any more blood tests taken by your doctor whilst you are in the hospice.

What are the possible disadvantages and risks of taking part?

There are no known side effects associated with the analyser. However, body analyser may interfere with medically inserted electric devices such as pacemakers and implantable cardiac devices. If you have such devices you will not be able to participate in the study.

What are the possible benefits of taking part?

The study will not help you directly. However, in the future the outcomes of study may enable clinicians to make better treatment decisions managing hydration in people with advanced cancer.

Expenses and payments

There will be no expenses or payments available for participants in this study.

What happens when the research study stops?

The clinical care received by participants would not be affected by the completion of the research study. At the end of the study a summary of the main research outcomes will be available for interested participants.

What will happen if I don’t want to carry on with the study?

If you do not feel that you are able to continue in the study you are free to change your mind and you will receive no further assessments. You can withdraw your consent at any time without giving a reason and without your clinical care being affected in any way.

Complaints and harm

If you have a concern about any aspect of this study, you should speak to the researcher who will do their best to answer your questions 0151 794 8972. If you
remain unhappy, please contact the hospice manager, Diane Barker on 0151 801 1400. In the event that something does go wrong and you feel you are harmed during the research you may have grounds for a legal action. Please contact the research sponsor, the University of Liverpool for further information.

**Will my taking part in this study be kept confidential?**

All information collected about you during the research will be kept confidential. Recorded information will be made anonymous and coded so you will be unidentifiable from the research documents. No personal information will be stored as part of the research study. All study information will be kept in a secure locked cabinet in the research offices of Marie Curie Palliative Care Institute Liverpool and will only be accessible to members of the research team. During the analysis phase, written information will be transferred to electronic records and will be encrypted to ensure confidentiality.

**Involvement of General Practitioner (GP)**

If you decide to participate in the study we will seek permission from you to notify your General Practitioner (GP). We will explain that your participation in this study will not alter your medical therapy and that no further treatment or monitoring is required on completion of the study.

**What will happen to the results of the research study?**

We hope to learn more about how water is regulated in people with advanced cancer and if this shows any association with their symptoms. We intend to publish the results in medical journals and present the findings to national and international research conferences in order to make sure that the message from this study are shared widely and appropriately. We will produce a summary of the research findings which will be circulated to interested participants. This study may lead to other research studies using a 'fluid drip' to see if this helps improve symptoms in advanced cancer.

**Who is organising and funding the research?**

The Marie Curie Palliative Care Institute Liverpool, University of Liverpool (MCPCIL) is responsible for organising the research.
Who has reviewed this study?

This proposal has been reviewed and approved by the North Wales Research Ethics Committee - West, which is a committee whose task it is to make that research participants are protected from harm. You can find out more about the work of Research Ethics Committees by visiting the National Research Ethics Service website at http://www.nres.npsa.nhs.uk.

If you would like any further information about this study please contact:

Dr Amara Nwosu
Research co-ordinator
Marie Curie Palliative Care Institute Liverpool (MCPCIL)
Dept of Molecular & Clinical Cancer Medicine
University of Liverpool
Cancer Research Centre
200 London Rd
Liverpool, L3 9TA
Tel: 0151 794 8972
Email: ami.nwosu@mariecurie.org.uk
Appendix 9: Screening questions to determine eligibility for study entry

1. Do you have cancer?
   Yes ☐ No ☐
   
   If NO ineligible for study

2. (a) Are you still receiving treatment for this cancer or is further treatment or investigation planned (e.g. surgical, radiotherapy, chemotherapy, procedures)?
   Yes ☐ No ☐
   
   If YES proceed to question 2(b)
   If NO proceed to question 3

   (b) If you are receiving treatment or you are due to receive treatment in the future, is the intention of this treatment palliative?
   Yes ☐ No ☐
   
   If NO ineligible for study

3. Do you have a pacemaker or an implantable cardiac device?
   Yes ☐ No ☐
   
   If YES ineligible for study

NOTE: Participants will be asked the above questions and medical records will be screened in order to confirm eligibility for study participation.
**Appendix 10: Consent form**

**Centre:** Marie Curie Hospice Liverpool

**Study Number:** RD 025

**Patient Identification Number for this study:**

CONSENT FORM

**Title of project:** Hydration in palliative cancer patients: the testing of a new assessment method

Name of Researcher: Dr Amara Nwosu

<table>
<thead>
<tr>
<th></th>
<th>Please tick box</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I confirm I have read and understand the information sheet date 19/08/13 (version 1) for the above study. I have had opportunity to consider the information, ask questions and have had these answered satisfactorily.</td>
</tr>
<tr>
<td>2</td>
<td>I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.</td>
</tr>
<tr>
<td>3</td>
<td>I agree to take part in the above study.</td>
</tr>
</tbody>
</table>

Name of patient

Name of witness

<table>
<thead>
<tr>
<th></th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date</td>
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<th></th>
<th>Signature</th>
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<tr>
<td></td>
<td>Date</td>
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</tbody>
</table>

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.
APPENDIX 11: Assessment schedule

- Questionnaire given to participant to complete (Appendix 9)
- Clinical examination (Appendix 10)
- Height assessment – portable stadiometer or tape measure if unable to stand upright
- Weight measurement using chair scale
- Fluid intake assessment and medication review
- Hydration body analyser assessment: bioelectrical impedance vector analysis
- Laboratory results accessed to record blood tests – serum urea and creatinine recorded

Has serum albumin, adjusted calcium (mmol/l) and serum osmolality (mosm/kg) been performed by the clinical team?

- Researcher records albumin adjusted calcium (mmol/l), serum osmolality (mosm/kg) from laboratory record
- Researcher gains consent from patient and clinical team to contact host laboratory to request the addition of these tests to the previous blood sample

Has urine osmolarity been recorded by the clinical team?

- Researcher gains consent from participant to obtain urine sample for analysis

Further serum urea and creatinine recorded by clinical

Patient consents for continued participation in the study?

- YES
- No further assessments

- NO
APPENDIX 12: Flowchart summary of research protocol

Potential participants admitted to Marie Curie Hospice

Potential participants identified

Potential participants approached

Informed consent for entry into the study

Blood test - serum urea and creatinine (and also, serum albumin, adjusted calcium (mmol/l) and serum osmolality (mosm/kg)) performed by the clinical team in previous 72 hours? Serum urea and creatinine are required for study entry. If the other investigations have not been performed, where possible, the research team will seek to have these tests added as an additional analysis to the existing blood sample.

Urine osmolarity taken by research team (if not performed by clinical team)

Baseline assessments
Hydration Questionnaire (Appendix 10)
Clinical examination (Appendix 11)
Height assessment
Weight measurement
Fluid intake assessment and medication review (APPENDIX 9)
Hydration body analyser assessment: bioelectrical impedance vector analysis (BIVA)

Further blood tests (serum urea and creatinine) done by clinical team (for example, for clinical monitoring purposes)?

YES

Follow on assessments (within 24 hours of blood test)
Hydration Questionnaire (Appendix 10)
Clinical examination (Appendix 11)
Fluid intake assessment and medication review (APPENDIX 9)
Hydration body analyser assessment: BIVA

NO

Patient discharged, death, little clinical value in blood tests (e.g. dying patients)

Is patient happy to continue participating in the study?

YES

NO

No further assessments
### Appendix 13: Data collection sheet for study assessments

Participant number: _________________________________

<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>SUBSEQUENT ASSESSMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date</strong></td>
<td></td>
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<tr>
<td><strong>Serum urea (mmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serum creatinine (µmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serum sodium (mmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serum calcium (mmol/l)</strong></td>
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<td></td>
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<tr>
<td><strong>Serum albumin (g/l)</strong></td>
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<td></td>
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<tr>
<td><strong>Serum osmolarity (mosm/kg)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Urine osmolarity (mosm/kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Resistance (R - Ohm)</strong></td>
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<tr>
<td><strong>Reactance (Xc)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>R/H Ohm/m</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Xc/H Ohm/m</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase angle (PA)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Body Mass Index - BMI (kg/m2)</strong></td>
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<td></td>
</tr>
</tbody>
</table>


Appendix 14: Demographic details collection sheet

Patient ID

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>DOB</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
</table>

**Asian or Asian British**
- White & Asian
- Chinese

**Indian**
- White & Black African
- Any other ethnic group

**Pakistan**
- White & Black Caribbean

**WHO performance status**

- **Any other Asian background**
- Any other mixed background
  - 0 Asymptomatic
  - 1 Symptomatic completely ambulatory
  - 2 Symptomatic, <50% in bed during the day
  - 3 Symptomatic, >50% in bed, but not bedbound
  - 4 Bedbound

**Primary site of cancer**

<table>
<thead>
<tr>
<th>Bladder</th>
<th>Bone</th>
<th>Brain</th>
<th>Breast</th>
<th>Colorectal</th>
<th>Cervical</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal</td>
<td>Leukemia</td>
<td>Lung</td>
<td>Mesothelioma</td>
<td>Myeloma</td>
<td>Non-Hodgkin Lymphoma</td>
<td>Hodgkin Lymphoma</td>
</tr>
<tr>
<td><em>Oesophageal</em></td>
<td>Ovarian</td>
<td>Pancreatic</td>
<td>Prostate</td>
<td>Skin</td>
<td>Stomach</td>
<td></td>
</tr>
<tr>
<td><em>Testicular</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presence of metastases

- Yes ☐ No ☐ If yes where

Vomiting and diarrhoea in previous 7 days?

- Yes ☐ No ☐

Disease co-morbidities (list):
Date of admission: __________________________
Date of discharge: __________________________
Date of death (if applicable): __________________________

**Medication list**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Oral fluid intake in previous 24 hours (tick box)**

<table>
<thead>
<tr>
<th>0-249 ml</th>
<th>250-499ml</th>
<th>500-749mls</th>
<th>750-999ml</th>
<th>&gt;1000ml</th>
</tr>
</thead>
</table>

**Volume of clinically assisted hydration administered in past 24 hours (tick box)**

<table>
<thead>
<tr>
<th>0-249 ml</th>
<th>250-499ml</th>
<th>500-749mls</th>
<th>750-999ml</th>
<th>&gt;1000ml</th>
</tr>
</thead>
</table>

**Has clinically assisted hydration been used in the previous 24-hours? Yes □ No □**

If yes, route clinically assisted hydration administration:

- Intravenous □ Subcutaneous □ Gastrostomy □

**Oral care regime in place? (tick box)**

<table>
<thead>
<tr>
<th>Mouthwash/oral rinse (e.g. chlorhexine)</th>
<th>Saliva replacement (e.g. oralbalance)</th>
<th>Saliva stimulant (e.g. pilocarpine)</th>
<th>Antibiotic/antifungal for mouthcare (e.g. fluconazole)</th>
<th>Oral protective gel (e.g. Gelclair)</th>
<th>Coated tongue treatment (e.g. vitamin C)</th>
<th>None</th>
</tr>
</thead>
</table>
## Appendix 15: The Anticholinergic Burden (ACB) scale

*(A total ACB scale score of three or more is considered clinically relevant)*

<table>
<thead>
<tr>
<th>ACB Score 1 (mild)</th>
<th>ACB Score 2 (moderate)</th>
<th>ACB Score 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimemazine</td>
<td>Amantadine</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Belladonna alkaloids</td>
<td>Amoxapine</td>
</tr>
<tr>
<td>Alverine</td>
<td>Carbamazepine</td>
<td>Atropine</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Cyclobenzapine</td>
<td>Benztrpine</td>
</tr>
<tr>
<td>Beclometasone dipropionate</td>
<td>Cyproheptadine</td>
<td>Chlorpheniramine</td>
</tr>
<tr>
<td>Bupropion hydrochloride</td>
<td>Loxapine</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Captopril</td>
<td>Meperidine</td>
<td>Clemastine</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Methotrimeprazine</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Cimetidine hydrochloride</td>
<td>Molindone</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Oxcarbazepine</td>
<td>Darifenacin</td>
</tr>
<tr>
<td>Codeine</td>
<td>Pethidine hydrochloride</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Pimozide</td>
<td>Dicyclomine</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>Diphenhydramine</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Doxepin</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Flavoxate</td>
<td></td>
</tr>
<tr>
<td>Diprydramole</td>
<td>Hydroxyzine</td>
<td></td>
</tr>
<tr>
<td>Disopyramide phosphate</td>
<td>Hyoscyamine</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Imipramine</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Meclizine</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>Nortriptyline</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Orphenadrine</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Oxybutynin</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Isosorbide preparations</td>
<td>Perphenazine</td>
<td></td>
</tr>
<tr>
<td>Loperamide</td>
<td>Procyclidine</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Promazine</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Promethazine</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Propentheline</td>
<td></td>
</tr>
<tr>
<td>Prednisone/Prednisolone</td>
<td>Pyrilamine</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>Scopolamine</td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Thoridazine (withdrawn)</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Tolterodine</td>
<td></td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>Trifluoperazine</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>Trihexyphenidyl</td>
<td></td>
</tr>
<tr>
<td>Triamterene</td>
<td>Trimipramine</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### References:
### Appendix 16: Symptoms of Dehydration Questionnaire – adapted from Burge 1991

APPENDIX 10 – Hydration questionnaire (adapted from Burge 1993)
Version 1; 01/06/2012
Assessment number

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Follow-on 1</th>
<th>Follow-on 2</th>
<th>Follow-on 3</th>
<th>Follow-on 4</th>
<th>Follow-on 4</th>
<th>Follow-on 5</th>
</tr>
</thead>
</table>

For each of the seven questions please use a cross (X) to mark one point on the line to indicate the average intensity of your symptoms over the past 24 hours.

1. **On average how thirsty have you felt during the last 24 hours?**
   - Not at all thirsty
   - [ ] ____________
   - Extremely thirsty

2. **On average, how would you rate the pain you have experienced during the last 24 hours?**
   - No pain
   - [ ] ____________
   - Worst pain imaginable

3. **On average, how dry has your mouth been during the last 24 hours?**
   - Not at all dry
   - [ ] ____________
   - Extremely dry

4. **On average, how nauseated have you been during the last 24 hours?**
   - Not at all nauseated
   - [ ] ____________
   - Extremely nauseated

5. **On average, how unpleasant has the taste in your mouth been in the last 24 hours?**
   - Not at all unpleasant
   - [ ] ____________
   - Extremely unpleasant

6. **On average, how fatigued have you been in the last 24 hours?**
   - Not at all fatigued
   - [ ] ____________
   - Extremely fatigued

7. **On average, how pleasant has it been to drink in the last 24 hours?**
   - Not at all pleasant
   - [ ] ____________
   - Extremely pleasant
Appendix 17: Clinical examination scoring system – adapted from Morita 2005

Clinical Examination guidance

For each patient indicate a score for each variable and then calculate the total hydration score:

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moisture of mucus membranes of mouth</td>
<td>Moist</td>
<td>Somewhat dry</td>
<td>Dry</td>
</tr>
<tr>
<td>Moist oral mucous membrane AND moist tongue palpation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moist oral mucous membrane WITH moist tongue OR moist mucous membrane with dry tongue on palpation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry oral mucous membrane PLUS dry tongue on palpation, with or without presence of tongue furrows, coated tongue or oral mucous lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moisture of the axilla</td>
<td>Moist</td>
<td>Dry</td>
<td></td>
</tr>
<tr>
<td>Moisture present on palpation</td>
<td></td>
<td>Dry on palpation</td>
<td></td>
</tr>
<tr>
<td>Sunkness of eyes</td>
<td>Normal</td>
<td>Slightly sunken</td>
<td>Sunken</td>
</tr>
<tr>
<td>Both eyes appear normal without recess in the socket</td>
<td></td>
<td>Both eyes appear slightly recessed in socket</td>
<td>Both eyes appear deeply completely recessed in socket</td>
</tr>
</tbody>
</table>

Total = /5
# Appendix 18: Oral health assessment chart

## ORAL HEALTH ASSESSMENT CHART

<table>
<thead>
<tr>
<th>Date of Admission</th>
<th>REVIEW DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Patients Age (yrs)
- 16-29
- 30-49
- 50-69
- 70+

### Nutritional State
- **GOOD** - Good appetite, well balanced diet. High fluid intake (>900ml)
- **FAIR** - Reduced appetite, unbalanced diet. Moderate fluid intake (500-900ml)
- **POOR** - Very poor appetite,ancerous/ malnourished. Low fluid intake (<500ml)
- **VERY POOR** - Nil/nutritional intake, Very low fluid intake (<200ml)

### Present Oral Condition
- **GOOD** - Mucosa intact, no infection, moist pink
- **FAIR** - Dry, no infection, mucosa intact
- **POOR** - Halitosis, Dry/red/swollen/dirty
- **VERY POOR** - Halitosis, Dry/red/swollen/dirty/Candida involvement (also malignant users or tumours)

### Airway
- **NORMAL**
- **HUMIDIFIED OXYGEN THERAPY**
- **NEBULISER THERAPY**
- **OPEN MOUTH BREATHING**

### Chewing/swallowing ability
- **FULL** - Health teeth, full muscle, well fitting dentures, pain free mouth
- **SLIGHTLY LIMITED** - Loose teeth/dentures
- **LIMITED** - Limited painful/weak muscles
- **VERY LIMITED** - Mainly loose teeth, ill fitting dentures/no dentures (having had them previously). Painful mouth. Very weak muscle e.g. CVA
- **IMMOBILE** - Semi conscious/unconscious

### Drug/Therapy Frequency of Administration
- **NEVER**
- **IRREGULARLY** (as required)
- **REGULARLY** (daily)
- **HOURLY OR INFUSION**

### Patient receiving chemotherapy
- **(3)**

### Patient receiving radiotherapy above shoulder level
- **(3)**

### Patient immunocompromised
- **(3)**

### TOTAL SCORE

### Nurses Signature

On present medication for sore mouth/thrust etc YES/NO If yes list below:

**Re-assess:** WEEKLY OR IF CONDITION CHANGES COMPLETE CARE PLAN ACCORDINGLY

192
Appendix 19: Bioelectrical Impedance Analysis (BIA) testing procedure

Testing Procedure

- The subject should not have exercised or taken a sauna within 8 hours of the study.
- The subject should refrain from alcohol intake for 12 hours prior to the study.
- The subject’s height and weight should be accurately measured and recorded.
- The subject should lie quietly during the entire test.
- The subject should remove the right shoe and sock and lie supine with the arms 30 degrees from the body and legs not touching.
- The electrode sites may need to be cleaned with alcohol, particularly if the skin is dry or covered with lotion.
- Attach the electrodes and patient cables as shown in the illustration.

Diagram showing electrode placement require for the bioelectrical impedance analysis test

Picture to show the appearance of bioelectrical impedance analysis in clinical practice
APPENDIX 20: Awarded grants

- Institute of Translational Medicine, University of Liverpool, £20,000, January 2013.
- Marie Curie Palliative Care Institute Liverpool (MCPCIL), £20,000, January 2013.
- Friends of the University of Liverpool, £10,000, July 2012.

APPENDIX 21: Awarded prizes

- Twycross Research Prize 2014, Association of Palliative Medicine, 2015.
- Early Researcher Award, European Association of Palliative Medicine (EAPC), 2015.
Appendix 22: Accepted conference abstracts

Oral Presentations

|-----------------------------------------------|--------------------------------------------------------|

Hydration in advanced cancer: the testing of a new assessment method

Background: Current hydration assessments methods are limited in cancer patients approaching death. Bioelectrical impedance analysis (BIA) is an accurate validated method of assessing body composition; however its clinical use in advanced cancer is uncertain.

Aim: To measure hydration in advanced cancer patients using BIA, in order to determine the relationship between symptoms, biochemistry and performance status.

Methods: A cross-sectional prospective analysis of advanced cancer patients within a specialist palliative care unit in Liverpool, UK.

BIA raw measurements, Resistance (R – Ohm), Reactance, (Xc – Ohm), total body water (TBW – through proxy measurement using height/resistance [Ht^2/R]), Phase angle (PA) and BIA vector analysis (BIVA) were used to compare for differences in hydration based on WHO performance status (0= asymptomatic, 4=bedbound), symptoms, physical examination and biochemistry.

Results: From a possible 97 patients, 78 (80%) provided consent to participate. Ht^2/R was lower in patients with a WHO performance status of 4 compared to those with a performance status <4 (mean 42.1 [SD 9.0] vs. 52.3 [14.6], p=0.002), and greater in those with clinically detectable oedema (mean 57 [SD 17.4] vs. 47.7 [12.4], p=0.027). Ht^2/R correlated negatively with thirst [r= -0.31, p=0.006], dry mouth [r= -0.294, p=0.009] and fatigue [r= -0.285, p=0.011]. BIVA showed significant difference in hydration between groups classified by the presence or absence of oedema (p=0.03) and dry mouth (p=0.04). There was no significant relationship between hydration (Ht^2/R and BIVA) vs. biochemical tests or between symptoms vs. biochemistry or performance status.

Conclusion: In advanced cancer, hydration (as measured by Ht^2/R and BIVA) relates to clinically measureable signs and symptoms. Further work is needed to determine whether BIA can be used to guide the management of fluid states in advanced cancer.
Background
There is limited scientific understanding of (de)hydration in advanced cancer. Consequently, decisions surrounding the administration of clinically assisted hydration (CAH) to dying cancer patients are challenging. Bioelectrical impedance analysis (BIA) has shown promise in assessing (de)hydration in various patient groupings, but evidence for its use in advanced cancer is limited.

Aim: To critically appraise existing methods of hydration status assessment and review the potential for BIA to assess (de)hydration in advanced cancer patients.

Method: A systematic review of literature was conducted. Searches were carried out on four electronic databases; conference abstracts and gray literature were searched by hand. Studies reporting (de)hydration assessment (biochemical tests, physical examination, symptom assessment, and bioelectrical impedance) in advanced cancer patients were included.

Results: Fifteen articles were identified. Clinical examination and biochemical tests are standard methods of assessing (de)hydration; however, limitations exist with these in advanced cancer. There is disagreement over the evidence for commonly associated dehydration symptoms in advanced cancer. BIA may have a role in evaluating (de)hydration; however, no studies of using this technology to assess hydration in advanced cancer have been conducted.

Conclusions: The benefits and burdens of providing CAH in dying cancer patients are unclear. BIA shows promise as a hydration assessment tool but requires further study in advanced cancer. Innovative research methodologies using BIA, combined with regression analyses of biochemical and symptom indications, may potentially improve scientific knowledge of (de)hydration and patient care.

Poster Presentations


European Association of Palliative Care 8th International World Congress, Lleida, Spain, 5-7th June 2014.

Background: Current hydration assessments methods are limited in cancer patients approaching death. Bioelectrical impedance analysis (BIA) is an accurate validated method of assessing body composition; however its clinical use in advanced cancer is uncertain.
Aim: This study aims to measure hydration in advanced cancer patients using BIA, in order to determine the relationship between symptoms, biochemistry, and performance status.

Methods: A cross-sectional prospective analysis of advanced cancer patients within a specialist palliative care unit in Liverpool, UK. BIA measurements: Resistance (R – Ohm), Reactance, (Xc – Ohm), total body water (TBW – through proxy measurement using height/resistance [Ht²/R]), Phase angle (PA) and BIA vector analysis (BIVA) were used to compare for differences in hydration based on WHO performance status (0= asymptomatic, 4=bedbound), symptoms, physical examination and biochemistry.

Results: From a possible 118 patients, 90 (76.3%) provided consent. Ht²/R was lower in patients with a WHO performance status of 4 compared to those with a performance status <4 (mean 43.0 [SD 9.0] vs. 53.6 [SD 15.9], p=0.001), and greater in those with clinically detectable oedema (mean 60.37 [SD 19.2] vs. 47.8 [11.8], p=0.004). Ht²/R correlated negatively with thirst [r= -0.29, p=0.006], dry mouth [r= -0.336, p=0.001], nausea [r= -0.226, p=0.032], unpleasant taste [r= -0.282, p=0.007], fatigue [r= -0.315, p=0.002]. BIVA showed significant difference in hydration between groups classified by the presence or absence of oedema (p=0.0036), and dry mouth (p=0.01). There was no significant relationship between hydration (Ht²/R and BIVA) vs. biochemical tests or between symptoms vs. biochemistry or performance status.

Conclusion: In advanced cancer, hydration status (as measured by Ht²/R and BIVA) relates to clinically measureable signs and symptoms. Further work is needed to determine whether BIA can be used to guide the management of fluid states in advanced cancer.


Background: There is limited understanding of hydration states in advanced cancer, and little evidence to inform management. Consequently, inappropriate management may cause patient harm and carer distress. Current hydration assessments methods are limited in cancer, partly due to patho-physiological differences compared to non-cancer. Bioelectrical impedance analysis (BIA) is a novel, accurate method of assessing body composition; however its use in advanced cancer is uncertain.

Methods: This study will determine the feasibility of BIA in the assessment of cellular hydration in advanced cancer, in order, to explore relationships between physical symptoms; biochemical and physiological parameters of hydration. This
will involve a longitudinal observational analysis of hospice in-patients with advanced cancer.

Results: Since December 2012, of the 74 eligible patients, 71 (95.9%) agreed to discuss the study with the researcher, with 58 (78.3%) providing consent for study participation. Ten (13.5%) patients agreed to take part initially, but were too ill at time of assessment; two patients (2.7%) were discharged before an assessment could take place. Four patients (5.4%) declined participation in the study.

The results demonstrate significant correlations between Resistance and creatinine \( r=0.272, n=58, p=0.039 \); Resistance and eGFR \( \rho=-0.289, n=58, p<0.028 \); Reactance and creatinine \( r=0.267, n=58, p=0.043 \). Intracellular water was found to be linked with thirst \( \rho=-0.470, n=20, p=0.037 \) and mucous membrane moisture \( \rho=-0.488, n=20, p=0.029 \). Biochemical dehydration was associated with significantly worse survival compared to non-dehydrated patients.

Conclusions: BIA may be useful in exploring associations between physiological measurements of hydration and symptoms. Vector transformation of BIA data (BIVA) will be undertaken to compare this data with other populations.


Background: There is limited understanding of hydration states in advanced cancer, and little evidence to inform management. Consequently, inappropriate management may cause patient harm and carer distress. Current hydration assessments methods are limited in cancer, partly due to patho-physiological differences compared to non-cancer. Bioelectrical impedance vector analysis (BIVA) is a novel, accurate method of assessing body composition.

Aim: To determine the feasibility of BIVA, as a method, of assessing cellular hydration in advanced cancer.

Methods: Longitudinal observational cohort analysis of advanced cancer hospice patients. Hydration status evaluated through: biochemical measures, BIVA, physical examination and self-reported symptoms.

Results: Preliminary analysis of 29 patients demonstrates significant correlations between intracellular water and various symptoms clusters.

Conclusions: BIVA may be useful in exploring associations between physiological measurements of hydration and symptoms. Future analyses will explore associations between bio-impedance assessments and survival.
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Background: There is limited scientific understanding of (de)hydration in advanced cancer. Consequently, decisions surrounding the administration of clinically assisted hydration (CAH) to dying cancer patients are challenging. Bioelectrical impedance analysis (BIA) has shown promise in assessing (de)hydration in various patient groupings, but evidence for its use in advanced cancer is limited.</td>
<td></td>
</tr>
</tbody>
</table>

Aim: To critically appraise existing methods of hydration status assessment and review the potential for BIA to assess (de)hydration in advanced cancer patients.  

Methods: Systematically structured review of literature. Searches were carried out on four electronic databases. Studies reporting (de)hydration assessment (biochemical tests, physical examination, symptom assessment, bio-electrical impedance) in advanced cancer patients were included.  

Results: Eleven articles were identified. Clinical examination and biochemical tests are standard methods of assessing (de)hydration; however, limitations exist with these in advanced cancer. There is disagreement over the evidence for commonly associated dehydration symptoms in advanced cancer. BIA may have a role in evaluating (de)hydration; however, no studies of using this technology to assess hydration in advanced cancer have been conducted.  

Conclusions: The benefits and burdens of providing CAH in dying cancer patients are unclear. BIA shows promise as a hydration assessment tool but requires further study in advanced cancer. Innovative research methodologies using BIA, combined with regression analyses of biochemical and symptom indications, may potentially improve scientific knowledge of (de)hydration and patient care.  

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
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<td></td>
</tr>
</tbody>
</table>

Aim: To critically appraise existing methods of hydration status assessment and review the potential for BIA to assess (de)hydration in advanced cancer patients.  

Methods: Systematic review of literature.  

Results: Eleven articles were identified. Clinical examination and biochemical tests are standard methods of assessing (de)hydration; however, limitations exist with these in advanced cancer. There is disagreement over the evidence for commonly associated dehydration symptoms in cancer. Bioelectrical impedance vector
analysis (BIVA) may have a role in evaluating (de)hydration but evidence for its use in cancer is limited.

Conclusions: BIVA but requires further study in advanced cancer. Innovative research methodologies using BIVA may potentially improve scientific knowledge of (de)hydration in cancer patients.
Appendix 23: Publications


Patients want to be involved in end-of-life care research

Advances in multimodal cancer-directed treatment have improved survival for metastatic cancer patients. In the Western world the combination of various demographic, health-related and sociological factors will contribute to increased comorbidities and mortality over the next decade. A careful, evidence-based approach is necessary to address the inevitable challenges, which will be posed by an increasingly aged population that will require supportive care towards the end of their lives.1 Further investment in palliative care research is required to generate the evidence which will improve the care delivered to patients approaching death.2 Currently, funding for end-of-life and palliative care research is inadequate. Data on UK research funding by National Cancer Research Institute partners in 2010 show that just 0.24% was allocated to palliative and end-of-life care research. Similarly, in 2010 the US National Cancer Institute only awarded 1% its funding to palliative care research.2

Research involving patients who are approaching death is methodologically and ethically challenging. This group of patients often have a significant symptomatic burden, including pain, fatigue and psychological distress. Researchers may struggle to engage and recruit participants due to concerns about the ability of patients to comply with assessments and provide consent. Consequently, low levels of recruitment, small sample sizes and high attrition rates often have a deleterious impact on the methodological quality of research.3 However, there is developing evidence which demonstrates that patients are keen to be involved in palliative care research.4

In light of these issues, we report the preliminary results of a pilot study using bioelectrical impedance analysis to assess hydration states in advanced cancer inpatients based within a specialist palliative care unit within Liverpool, UK. Participating patients are assessed using bioelectrical impedance analysis, undergo a clinical examination and complete a self-reported symptom questionnaire. Since December 2012, of the 80 eligible patients, 78 (97.5%) agreed to discuss the study with the researcher, with 61 (76.3%) providing consent for study participation. Eleven (13.7%) patients agreed to take part initially but were too ill at time of assessment. Two (2.5%) were discharged prior to study assessments; so far, only six patients (7.5%) have declined to participate in the study. As in other published research, all enrolled patients stated a desire to help others as a motivating factor for participating in the research study.4

In line with the published literature, our experience within this study suggests that palliative care patients are keen to be involved in research and that their experience is positive.5 Our data suggest that a good level of recruitment to studies involving palliative patients is possible. This is noteworthy, as patients in specialist palliative care units are more likely to have more advanced disease and symptom burden compared to those within general medical and oncology units. Researchers, funders and policy makers should be encouraged, as patient participation in research will help to identify and address patient-centred priorities at the end of life.

REFERENCES

Hydration in Advanced Cancer: Can Bioelectrical Impedance Analysis Improve the Evidence Base? A Systematic Review of the Literature

Amara Callistus Nwosu, MBChB, MRCP, Catriona R. Mayland, MBChB, MD, FRCP, Stephen R. Mason, PhD, PGCE, BA, Andrew F. Khodabukus, MBChB, BSc, MRCP, Andrea Varro, PhD, MD, and John E. Ellershaw, MB BCh, MA, FRCP

Marie Curie Palliative Care Institute Liverpool (A.C.N., C.R.M., S.R.M., A.F.K., J.E.E.); School of Physiological Sciences (A.V.), Institute of Translational Medicine, University of Liverpool; and Aintree University Hospitals NHS Foundation Trust (C.R.M.), Liverpool, United Kingdom

Abstract

Context. Decisions surrounding the administration of clinically assisted hydration to patients dying of cancer can be challenging because of the limited understanding of hydration in advanced cancer and a lack of evidence to guide health care professionals. Bioelectrical impedance analysis (BIA) has been used to assess hydration in various patient groupings, but evidence for its use in advanced cancer is limited.

Objectives. To critically appraise existing methods of hydration status assessment in advanced cancer and review the potential for BIA to assess hydration in advanced cancer.

Methods. Searches were carried out in four electronic databases. A hand search of selected peer-reviewed journals and conference abstracts also was conducted. Studies reporting (de)hydration assessment (physical examination, biochemical measures, symptom assessment, and BIA) in patients with advanced cancer were included.

Results. The results highlight how clinical examination and biochemical tests are standard methods of assessing hydration, but limitations exist with these methods in advanced cancer. Furthermore, there is disagreement over the evidence for some commonly associated symptoms with dehydration in cancer. Although there are limitations with using BIA alone to assess hydration in advanced cancer, analysis of BIA raw measurements through the method of bioelectrical impedance vector analysis may have a role in this population.

Conclusion. The benefits and burdens of providing clinically assisted hydration to patients dying of cancer are unclear. Bioelectrical impedance vector analysis shows promise as a hydration assessment tool but requires further study in...
advanced cancer. Innovative methodologies for research are required to add to the evidence base and ultimately improve the care for the dying. J Pain Symptom Manage 2013;46:433–446. © 2013 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

**Key Words**
Palliative care, cancer, hydration, dehydration, bioelectrical impedance analysis, clinically assisted hydration

**Introduction**

The role of hydration in causing or alleviating suffering in patients with advanced cancer is poorly understood and remains controversial. Most patients dying of cancer have reduced oral intake in their last days of life. This may be related to either cancer or its treatment, and reasons include dysphagia, anorexia, nausea or vomiting, or mechanical problems such as bowel obstruction. Accordingly, the subject of clinically assisted hydration (CAH) is emotive among patients and their carers, with the omission or withdrawal of CAH potentially viewed as hastening death in some instances. Decisions surrounding the administration of CAH to patients at the end of life can be challenging, with many health care professionals, patients, and carers presenting differing opinions on appropriate management.

Dehydration

Physiologically, dehydration has been defined as deficit of total body water (TBW) that is predominantly intracellular. This process is associated with hypernatremia, an elevated serum osmolarity, which in turn stimulates the sensation of thirst from the thirst center. Patients with advanced cancer may not fit this pattern because of differences in their fluid requirements and disease pathophysiology, when compared with noncancer populations. In cancer, intracellular dehydration is associated with proteolysis and cachexia and leads to an increase in antidiuretic hormone (ADH) level through stimulation of osmoreceptors or from direct release from the tumor. Furthermore, weight loss, decreased renal perfusion, and cachexia are associated with a loss of intracellular water and solutes affecting hypothalamic osmoreceptors, which in turn stimulates ADH release.

ADH increases the water permeability of the distal tubule and collecting duct in the kidney, promoting water absorption and the maintenance of serum osmolarity and sodium at subnormal levels. Consequently, an abnormally low osmolarity may cause symptoms such as nausea and confusion, which have been associated with dehydration.

Most patients with cancer suffer from hypotension rather than hypernatremia. Hypotension results from sodium loss in excess of free water, resulting in a low sodium and serum osmolarity. Furthermore, certain medications such as selective serotonin reuptake inhibitors and nonsteroidal anti-inflammatory drugs also are associated with hyponatremia and are frequently given to patients with cancer for symptom management.

Clinical studies suggest that patients dying of cancer may achieve adequate hydration with much lower volumes of water than those recommended for the average medical or surgical patient. This may result from differences in body composition, such as decreased body weight because of cachexia and decreased clearance of free water caused by a variety of mechanisms. For example, patients with advanced cancer may have reduced insensible water losses resulting from a reduction in their
physical activity. Typically, hydration studies are based on noncancer populations and subsequent research findings may not extrapolate to patients with cancer. Consequently, proffered definitions of dehydration in patients with cancer vary throughout the literature, with authors using different combinations of clinical parameters as diagnostic criteria. The lack of uniformity in definitions complicates study comparisons and makes decisions regarding the use of CAH difficult for clinicians. There is a need for further study in this area to address the limited research base.

Novel methods of hydration assessment, such as bioelectrical impedance analysis (BIA), have been used in some areas (e.g., in the assessment of the fluid states of edematous patients with renal failure receiving dialysis), but evidence for its use in advanced cancer is limited. BIA is a safe, noninvasive, bedside method of assessing hydration.

**Aims**

The aims of this review are:

1. To critically appraise the existing methods of assessing hydration status in patients with advanced cancer, namely physical examination and biochemical measures;
2. To identify dehydration-related symptoms in patients with advanced cancer; and
3. To review the use of BIA in the assessment of hydration and to discuss its potential use in patients with advanced cancer.

**Methods**

A search strategy was developed for finding relevant publications in electronic literature databases. In January 2012, four electronic databases were searched (MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Scopus) using combinations of the key words: palliative care, terminally ill, hospice, terminal care, dehydration, water-fluid balance, fluid balance, bioelectrical impedance, cancer, tumor, carcinoma, and malignancy. The search was limited to English language literature published between 1960 and 2012. The search strategy for MEDLINE is shown in Table 1 and was adapted for the other databases.

Bibliographies of relevant articles were manually searched to identify more articles for potential inclusion. Additionally, a hand search of the most recent issues (January 2010 to July 2012) of 12 relevant peer-reviewed journals was conducted: *Journal of Pain and Symptom Management, Journal of Palliative Care, Palliative Medicine, Journal of Palliative Medicine, New England Journal of Medicine, Lancet Oncology, British Medical Journal (BMJ), BMJ Supportive and Palliative Care, The Journal of the American Medical Association, Annals of Internal Medicine, Nutrition, and American Journal of Clinical Nutrition*. The gray literature was searched; this literature comprised abstracts from the *American Academy of Hospice and Palliative Medicine conferences (2010–2012), the European Association of Palliative Care conferences (2010–2012), the Palliative Care Congress (2012), the International Congress of Palliative Care (2010), and the Marie Curie Research Conferences (2011–2012)*. To obtain further information about the gray literature abstracts that were selected for inclusion in this study, the authors of these studies were contacted (by e-mail) and asked to provide more information about the research. Further details of studies included in this review are presented in Table 2 (available on jpsmjournal.com).

**Selection Criteria**

One reviewer (A. C. N.) used a stepwise procedure to identify relevant studies. Studies addressing (de)hydration assessment (physical examination, biochemical measures, symptom assessment, and BIA) in patients with advanced cancer were eligible for inclusion in the review.

### Table 1

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<tr>
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<td>(((cancer) OR neoplasms) OR tumor) OR carcinoma OR malignancy</td>
</tr>
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<td>#3</td>
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<td>#5</td>
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</tr>
<tr>
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<td>#1 AND #2</td>
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</table>
For the purposes of this study, advanced cancer was defined as a diagnosis of cancer where no further curative treatment is possible, which may be associated with metastases (histological or radiological). Articles were excluded if the studies were not in English or if they primarily reported on pediatric populations.

**Data Extraction**

Data were extracted using a standard form to record the following themes: purpose of study, study design, participants, exclusions, sample size and statistics, dehydration definition(s), outcome measure, and study methods. The first author extracted the data from studies and discussed the results with A. F. K., S. R. M., and C. R. M. Reviewers were not blinded for authors, institutions, or journals of publication.

**Quality Assessment**

Because the review included studies with both quantitative and qualitative elements, a multimethods assessment tool, devised by Hawker et al. was used to evaluate the study quality. This assessment tool comprises nine areas; each area was rated on a four-point scale from one (very poor) to four (good). The areas covered were abstract and title, introduction and aims, methods and data, sampling, data analysis, ethics and bias, results, transferability or generalizability, and implications and usefulness. Consequently, each article was given a total score (maximum of 36 = good and a minimum of 9 = very poor) based on the methodological rigour. The methodological quality was assessed independently by A. C. N. and A. F. K. Both authors agreed on the quality assessment of all studies. Data were stored and analyzed using Statistical Software Package for the Social Sciences (SPSS version 20.0; IBM SPSS Inc., Chicago, IL). The methodological quality score is ordinal in nature; consequently, Spearman’s rank correlation coefficient was chosen to measure pairwise correlations of scores between assessors.

**Results**

Results of the literature search are summarized in Fig. 1. The initial literature search using the keywords outlined in the Methods section returned 334 articles. A total of 316 of these articles were rejected after the review of the abstract as not relevant. The remaining 18 articles were examined by our inclusion and exclusion criteria. Three articles were excluded as they primarily reported noncancer populations, resulting in the inclusion of 15 studies in the review. The methodological quality of the selected studies ranged between 22 and 36. Spearman’s rank correlation coefficient demonstrated a statistically significant level of agreement between assessors ($r_s = 0.846, P < 0.0001$). Commonly, sample size calculations were not conducted and some studies lacked descriptive information about the context, setting, and characteristics of the included (and excluded) patients. Consequently, several studies received lower scores regarding their potential transferability and generalizability. However, no study made any claim that its data could be generalized beyond the particular population of interest.

**Physical Examination**

The clinical assessment of hydration, through the process of physical examination, is a measure of the extracellular fluid compartment (i.e., extracellular water content, skin turgor, jugular venous pressure, and pulse). However, as dehydration prominently describes an intracellular process, clinical assessment is unable to diagnose intracellular dehydration. There are no routine bedside technologies that measure fluid in the intracellular space. Aware of this problem, authors have attempted to address the issue by creating a distinction between dehydration defined physiologically from that derived from subjective clinical assessment. In these instances, the term clinical dehydration is generally used to encompass all types of deficit fluid as they appear in the clinical setting. This highlights the possible conflict between the clinical experience of dehydration compared with the biochemical and physiological definitions of dehydration commonly found in the literature.

Some authors have attempted to clarify which signs are clinically relevant in the assessment of dehydration in elderly and cancer populations. Noncancer studies have found certain variables to correlate with dehydration in elderly populations; these include tongue dryness, longitudinal tongue furrows, dry mucous membranes, upper body muscle weakness,
confusion, speech difficulty, sunken eyes, dry axilla, a fall in systolic blood pressure, reduced laxity of sternal skin turgor, and low body mass index.

Based on the outcomes of these studies, Morita et al. subsequently developed a dehydration score consisting of three variables (dryness of oral mucous membranes, axillary moisture, and sunkenness of eyes). This score was used to assess dehydration, in addition to assessments of delirium and peripheral edema, in a study of CAH volume and its association with symptoms in terminally ill cancer patients with abdominal malignancies. Dehydration scores were significantly lower in the patients receiving CAH in the last three weeks of life compared with the non-CAH group; however, use of CAH was associated with increases in peripheral edema. No significant difference in hyperactive delirium, communication capacity, bronchial secretions, agitation, myoclonus, or serum biochemistry was evident between the two groups. A similar study by the same authors examined the relationship between laboratory findings, artificial fluids, fluid balance, and clinical measures of dehydration in terminally ill patients with abdominal cancer. The authors found no statistically significant difference in the fluid balance in patients with an increased clinical dehydration score compared with those without. Myoclonus and sedation have been associated with dehydration in a study by Bruera et al., who demonstrated improvements in these variables during a randomized, controlled, double-blind trial involving dehydrated patients with cancer receiving CAH. However, these findings have not been replicated in other studies.

There is conflict over the accuracy of physical findings in assessing hydration in advanced cancer. Skin turgor has been shown to poorly correlate with dehydration as patients with cancer are prone to changes in subcutaneous tissue, which may create inaccuracy in its interpretation. Postural hypotension is identified as a feature of hypovolemia (low blood volume), but lacks sensitivity as a test for dehydration. This highlights how...
different definitions of dehydration may create difficulty in interpreting study outcomes. Furthermore, postural hypotension may not be suitable in assessing some patients with advanced cancer at risk for poor mobility, falls, and taking medications known to cause hypotension, for example opioids and diuretics. Variations in body mass caused by cachexia and edema may make body mass index measurements unsuitable.

Although part of a standard medical examination, capillary refill is only able to detect hypovolemia in children and lacks sensitivity in adults.

**Biochemical Measures**

Biochemical tests include the analysis of blood (obtained from venipuncture) and urine samples. A change in urine and blood chemistry provides clues to the underlying cause of hydration disturbances and helps the clinician identify potential treatments. Measures such as serum urea:creatinine ratio and urine:plasma osmolality ratio have been used to assess hydration status, with ratios of $\geq 100$ (mmol/mmol) and $\geq 1.2$, respectively, suggesting dehydration. Biochemical dehydration occurs when intracellular water is lost, leading to transmembrane water migration from the intravascular compartment under osmotic pressure and increased relative plasma sodium concentration. Electrolyte abnormalities, such as hyperkalemia, may suggest underlying causative factors of dehydration and may be useful prognostic indicators. Atrial natriuretic peptide (ANP) level lower than 15 pg/mL has been used to define dehydration in palliative care patients; however, the validity and reliability of this measure has not yet been determined. Observational studies have found that biochemical measures of dehydration poorly correlate with symptoms, such as thirst and dry mouth.

Biochemical investigations are performed for various reasons, including clinical monitoring, in advance of medical procedures, and assessment in response to change in the clinical condition of a patient. In these circumstances, abnormal renal function may prompt the clinician to consider the initiation of CAH; however, studies have shown that patients with advanced cancer may be prone to renal impairment at the end of life. The prevalence of pre-renal failure in cancer inpatients was 44% ($n = 27/62$) in a study by Guo et al., no difference in length of stay was evident between patients with renal failure compared with those with normal renal function. Biochemical measures alone may not be able to detect clinically meaningful hydration changes in patients with cancer, especially if measurements are performed without a record of the patient’s baseline renal function for comparison. Authors have demonstrated a worsening in renal function in patients with cancer approaching death, irrespective of whether CAH is administered or not. Therefore, in advanced cancer, static abnormal renal function measurements may provide incomplete assessments of hydration status. A prospective study by Waller et al. examining hydration indicators in patients found 87% ($n = 59/68$) of dying patients to be biochemically dehydrated. No difference in serum biochemistry or consciousness was found between patients receiving intravenous fluids compared with those who received no fluids. The authors conclude that there is no clinical benefit to the administration of intravenous fluids in terminally ill patients with cancer.

**Symptoms of Dehydration**

Previous research has attempted to determine if symptom burden is related to dehydration and, consequently, whether the use of CAH improves these symptoms. The first quantitative estimate of dehydration symptoms in advanced cancer was conducted by Burge in 1993. This study was a cross-sectional analysis of the symptoms of dehydration in 52 palliative care patients with cancer. A series of 100 mm visual analogue scale scores were used to evaluate the severity of seven symptoms (thirst, dry mouth, bad taste, nausea, pleasure in drinking, fatigue, and pain) experienced by patients. Fatigue was the most severe symptom (65% rated greater than 50 mm); dry mouth and thirst also were very prevalent (53.8% and 60% rated greater than 50 mm, respectively). There was no association between symptom severity and fluid intake, or between biochemical measures and thirst, a finding consistent with other studies. However, Cerchietti et al. demonstrated improvements in thirst and chronic nausea in symptomatic palliative care cancer patients with limited oral intake, randomized to receive either CAH or
standard medical therapy. Significant improvements in relief of thirst and chronic nausea were present in both groups at 24 hours; however, this effect was only maintained in the hydration group at 48 hours. There is little evidence to support the role of CAH in the management of delirium in advanced cancer.58,59 A statistical analysis of hospital inpatient data of 1125 patients with advanced cancer failed to demonstrate a relationship between hydration and delirium;60 this is a similar finding in other studies.2,35,61 However, hyperactive delirium was found to be more prevalent in patients with advanced abdominal cancers receiving small volumes of CAH (<1 L/d) compared with patients receiving larger volumes (>1 L/d).61

Studies assessing oral symptoms and dehydration have found mixed results. Dry mouth and thirst were highly prevalent in a study of 82 patients with cancer receiving palliative care at risk for dehydration.54 Of the 23 (28%) patients able to respond to the questions, 20 (87%) reported dry mouth and 19 (83%) complained of thirst. No association between thirst, dry mouth, respiratory tract secretions, and biochemical dehydration was found. Similarly, in a cohort of 88 palliative care patients, Morita et al.53 found thirst to be highly prevalent, but poorly associated with dehydration. Interestingly, the authors found that thirst was associated with water depletion (defined by ANP). However, a lack of validity and reliability of ANP and the arbitrary cutoff level defined by the authors may indicate that this area requires further study before definitive conclusions are drawn. The effect of CAH on sensation of thirst in 30 terminal cancer patients was evaluated by Musgrave et al.62 Nineteen patients were able to communicate thirst intensity, but no association between level of thirst, intravenous fluids, and biochemical parameters was demonstrated. Nakajima63 explored the influence of hydration on symptoms in a series of 75 patients with advanced abdominal cancer. The study found that CAH improved oral membranous signs of dehydration but worsened peripheral edema, ascites, and chest secretions. Yamaguchi et al.61 found no significant difference in symptom burden between patients receiving high volumes (>1 L/24 h) and low volumes (<1 L/24 h) of fluid in a multicenter, prospective, observational study of 161 patients with advanced cancer receiving CAH.

Bioelectrical Impedance Analysis

BIA is based on the flow of electrical current through the body, measured through the application of superficial skin electrodes.54 BIA is not a direct method of monitoring body composition and TBW requires prediction equations for analysis.27 Prediction equations have been developed using linear regression and adherence to some basic assumptions, including the shape of the body, the relationship between trunk and leg lengths, and the level of hydration (as lean body mass hydration is considered 73%) and fat fraction.27 No universal equation exists to accommodate different populations; therefore, specific validated equations need to be selected depending on age, ethnic group, and the clinical situation being studied.27 However, cancer (and other wasting diseases) reduces intracellular water through cachexia, such that the TBW derived from equations for normal populations will become less accurate.15

The limitations of BIA have been addressed by Piccoli65 by using an alternative method of interpreting the BIA information. Use of raw BIA measures can provide direct measurements of tissue cell hydration and integrity. These approaches are independent of regression equations or weight, and can be carried out even in situations where BIA assumptions are not met (e.g., in advanced cancer). These raw measurements comprise resistance (R—the restriction to the flow of electrical current through the body, primarily related to the amount of water present in tissue) and reactance (Xc—resistive effect produced by the tissue interfaces and cell membranes) measurements (Fig. 2). Two indicators of clinical significance can be derived from the raw measurement; one is phase angle and the other is a plot of the impedance vector against a known distribution (bioelectrical impedance vector analysis—BIVA).27,66,67

Phase Angle. Phase angle is a derived measure obtained for the relation between the direct measures of resistance and reactance and can be calculated from raw BIA measurements (Fig. 2).98 Part of the measured electrical current is stored by the cell membranes, which act
as capacitors, creating a phase shift, quantified geometrically as phase angle.²⁷ Phase angle has been used as a prognostic marker in various patient groups, including human immunodeficiency virus,⁶⁹,⁷⁰ dialysis patients,⁷¹–⁷³ breast cancer,⁷⁴ lung cancer,⁷⁵ colorectal cancer,⁷⁶ and pancreatic cancer.⁷⁷ Recently, studies have used the technology to evaluate hydration in advanced cancer; for example, Davis et al.¹⁵ performed a prospective observational study using BIA in patients with advanced cancer receiving CAH. BIA was done for three consecutive days from initiation of CAH. The authors found that a greater phase angle on Day 1 of CAH predicted better survival; however, a rise in phase angle (indicating increased reactance and the distribution of fluid to the intracellular compartment) during CAH predicted shorter survival. The authors propose that an increase in phase angle during CAH reflects pre-existing intracellular dehydration, which occurs in patients who are more likely to have cachexia-anorexia syndrome, and hence, a worse prognosis compared with those without a phase angle rise during CAH. This may suggest that phase angle may be able to assist in prognostication and may highlight underlying physiological differences among patients with cancer receiving CAH. Crawford et al.⁷⁸ used BIA to show that elevated metabolic rate and accumulation of body fluids were indicators of poor prognosis in a series of palliative care patients with cancer. Although interesting, these studies focus on survival and do not explore issues regarding hydration assessment or the appropriateness of using CAH in these patients.

Bioelectrical Impedance Vector Analysis. BIVA, in a fashion similar to the electrocardiogram, uses graphical vectors to provide a visual analysis of BIA data.⁶⁷ Using this method, impedance (Z) is plotted as a vector from its components R (x-axis) and Xc (y-axis), after being standardized by height (H) (Fig. 3). Confidence interval of the mean vector can be plotted to allow statistical analysis and comparison in (and between) population groups (Fig. 4). The advantage of this method is that it allows information to be obtained simultaneously about changes in tissue hydration or soft tissue mass, independent of regression equations, or body weight. Therefore, BIVA readings can be interpreted accurately even if patients are at extremes of weight or volume distribution. BIVA measurements can be compared with reference populations to enable comparisons with healthy populations and other diseases. Changes in the shape and direction of plotted vectors (vector migration) on repeated measurements in the same individual allow change in hydration status over time to be recorded.²⁷ BIVA has previously been used to monitor hydration change in edematous patients receiving hemodialysis and may provide a way to monitor change in hydration over time in patients with advanced cancer (e.g., during the dying phase). Although BIVA has been used to study hydration in different diseases (e.g., renal failure, cholera, and congestive cardiac failure),²⁶,⁷⁹–⁸⁶ and to undertake general body composition assessments in lung cancer,⁸⁵,⁸⁶ Fig. 2. Graphical representation of bioelectrical impedance analysis raw measurements: impedance, reactance, resistance, and phase angle.

Fig. 2. Graphical representation of bioelectrical impedance analysis raw measurements: impedance, reactance, resistance, and phase angle.

![Graphical representation of bioelectrical impedance analysis raw measurements](image)

![Example of a bioelectrical impedance vector analysis plotted on the RXc graph with 95%, 75%, and 50% tolerance ellipses. Reproduced with permission from Piccoli et al.](image)
and cancers of the head and neck,
symptom in patients with cancer. Dry mouth and thirst are common in cancer; however, these variables may be unreliable indicators of (de)hydration as a result of their association with other factors. One study suggests the significance of thirst when serum ANP is used to define dehydration, but the validity and reliability of this measure has not yet been determined. Despite a greater prevalence of hyperactive delirium in patients receiving reduced volumes of CAH compared with larger volumes, the evidence is poor for the influence of hydration on delirium in advanced cancer. Overall there is a lack of clinical assessment tools to evaluate hydration in advanced cancer and unclear data about which symptoms are most related to dehydration. These findings, combined with the unclear benefits and burdens of CAH, make decisions about the use of CAH challenging for health care professionals.

BIA is able to assess body composition and has been used as a prognostic marker in cancer studies. One study demonstrated that phase angle increase in patients receiving CAH was associated with increased mortality. This may suggest that patients with cancer differ physiologically in their ability to handle fluids, with some more prone to adverse effects than others. The study is limited by small numbers of patients and a lack of standardization of the type of fluid prescribed and the rate of volume replacement. If a true difference exists, this may highlight the importance for clinicians to consider these factors when administering CAH. Furthermore, studies using BIA may potentially be a tool to enable clinicians to better understand hydration in advanced cancer. BIA alone is limited in its ability to assess hydration in advanced cancer; however, interpretation using BIVA improves the accuracy of measuring static and dynamic hydration states. The noninvasive nature of the technology may be popular for researchers keen to use novel methodologies for assessing hydration in advanced cancer. Consequently, BIVA shows promise as a method for assessing hydration and could be potentially used to further scientific study into the relationship between hydration and related symptoms. However, further study is required to establish whether measurements of fluid distribution in advanced cancer, as determined by BIA and BIVA, are clinically relevant.

This review is unique in highlighting the potential of BIVA to assess hydration in patients with advanced cancer. We have identified a lack of evidence relating to the assessment and symptomatic treatment of dehydration in cancer, a finding consistent with similar studies in this area.

We recognize that there are several limitations with this review. Although hand searching of relevant journals and gray literature took place, this was limited to the past two years, and the abstract lists were unavailable for some conferences; consequently, there is the potential that data were excluded from this review. Although a structured process for identification and inclusion of articles was adopted, the reviewers were not blinded to the authors and institutions of the reviewed articles. Consequently, there is risk of the reviewers’ own bias relating to articles included or excluded from the review. Many of the included studies were small, descriptive, and underpowered studies with differing definitions of dehydration. These diagnostic definitions may have been based on biochemical criteria, clinical markers, or a combination of both; therefore, comparisons between the studies are difficult. Studies involving patients with advanced cancer present ethical and methodological challenges that are compounded by the difficult issue of (de)hydration. Consequently, researchers and ethics committees may still be learning about suitable approaches for this subject, which may currently limit the number of research studies that were available for inclusion in this review. BIA and BIVA have been used to assess body composition in several populations; however, there is a lack of studies using this technology to report on clinically relevant outcomes (e.g., symptom burden, survival, and the effect of CAH on these parameters) in advanced cancer. Additionally, we were unable to identify any literature reporting on the use of BIVA to evaluate hydration in advanced cancer. The intervention studies involving CAH used various routes of administration and different fluid preparations over differing time periods at different stages of the subjects’ illness. Although the outcomes of these studies are interesting, the lack of harmony between methodology and...
outcomes limits the ability of this review to synthesize data.

A lack of consensus as to how to assess hydration in advanced cancer makes decisions regarding the use of CAH difficult for the clinician. Further complexity is added because of the limited number of high quality studies assessing the benefits and burdens of CAH for this population. This review has highlighted how patients with advanced cancer may experience some benefits from receiving CAH, such as improvements in sedation, myoclonus, and nausea. However, there is the potential to cause harm, in terms of worsening symptoms of fluid retention (e.g., peripheral edema, pleural effusion, and ascites). On the basis of insufficient evidence, we are limited in our ability to draw definitive recommendations. Clinicians, therefore, are advised to make assessments based on the perceived benefits, risks, and burdens to the individual. The clinician should be familiar with existing methods of hydration assessment and be aware of their limitations.

Further research to clarify the symptoms associated with dehydration and to highlight the benefits and burdens of CAH in patients with advanced cancer is required. Future studies need be appropriately powered, with clear definitions of (de)hydration. These studies will require innovative methodologies, for example, using advance consent of patients. Core outcome sets for hydration studies should be agreed to enable clinicians to compare, contrast, and synthesize the results of the studies more effectively. The assessment of (de)hydration should be conducted in a variety of terminal diagnoses at different stages of the illness trajectory.

Currently, no studies have used BIVA for the assessment of hydration in the advanced cancer population. Pilot studies using BIVA are required to determine its feasibility and efficacy before conclusions may be drawn. If feasible, BIVA may have a role in evaluating hydration in advanced cancer and improving knowledge of hydration in dying patients. BIVA could be used in combination with other hydration assessment methods to determine the scientific association of symptoms with dehydration, facilitating the creation of core outcome measures for hydration, which can further support intervention studies using CAH. Consequently, future studies could use BIA and BIVA to determine its usefulness in predicting and monitoring clinical response to treatments (such as CAH) and survival through static and longitudinal assessments.

Conclusions

Hydration is an important area of care for patients with advanced cancer. Limitations exist with current hydration assessment methods and there is a lack of consensus of the symptoms associated with dehydration. The benefits and burdens of providing CAH to patients dying of cancer are unclear. BIVA shows promise as a hydration assessment tool but requires further study in advanced cancer. Innovative methodologies for research are required to add to the evidence base and ultimately improve the care for the dying.

Disclosures and Acknowledgments

The authors declare no conflicts of interest. The authors thank Suzanne Beck who assisted with the literature search for this review article.

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<th>Outcome Measure</th>
<th>Methods</th>
<th>Appraisal Total Score</th>
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<tr>
<td>Morita et al.</td>
<td>To explore systematically the dehydration volume and fluid retention symptoms in the last 3 wk of life in terminally ill patients with abdominal malignancies.</td>
<td>Multicenter, prospective, observational study</td>
<td>226 Fourteen oncology units, 19 palliative care units (PCUs), and 4 home-based palliative care programs in Japan.</td>
<td>Age ≥20 y &lt;br&gt; Life expectancy ≥3 mo &lt;br&gt; Incurable malignancy of lung or abdominal origin (excluding hepatic malignancies)</td>
<td>Degree of dehydration defined on basis of three physical findings</td>
<td>Analyses of data collected: &lt;br&gt; Patients classified into two groups; the hydration group (n = 99) who received ≥1 L or more of artificial hydration per day both 1 and 3 wk before death, and the nonhydration group (n = 167) who did not.</td>
<td>Percentage of patients with deterioration in dehydration score in final 3 wk of life significantly higher in nonhydration group compared with hydration group (35% vs. 14%, P = 0.002). Fluid retention symptoms increased significantly in hydration group compared with nonhydration group: edema (44% vs. 29%, P = 0.039), ascites (29% vs. 8.4%, P &lt; 0.001), pleural effusion (15% vs. 5.4%, P = 0.016). No significant difference in degree of bronchial secretions, hyperactive delirium, communication capacity, agitation, monodramia, or bedsores.</td>
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<td>Degree of dehydration defined on basis of three physical findings</td>
<td>Secondary analyses of data collected: &lt;br&gt; Laboratory data, clinical assessment data, fluid balance, and oral intake. &lt;br&gt; Patients classified into two groups: the hydration group (n = 44), who received ≥1 L or more of artificial hydration per day both 1 and 3 wk before death, and the nonhydration group (n = 81) who did not.</td>
<td>The mean albumin level 1 wk before death was significantly lower in the hydration group than in the nonhydration group, and the interaction between hydration group and the albumin level. There was no significant difference between the groups in the mean blood urea nitrogen/creatinine (BUN/Cr), sodium, or potassium levels 1 wk before death.</td>
<td>30</td>
<td>The mean albumin level 1 wk before death was significantly lower in the hydration group than in the nonhydration group, and the interaction between hydration group and the albumin level. There was no significant difference between the groups in the mean blood urea nitrogen/creatinine (BUN/Cr), sodium, or potassium levels 1 wk before death.</td>
</tr>
</tbody>
</table>
The calculated fluid balance was not significantly different between the patients with deterioration in scores of dehydration, edema, ascites, and pleural effusion during the last 3 wk and those without.

Guo et al. To determine the prevalence of pre-renal anemia in a cancer rehabilitation patient population. To evaluate the relationship of pre-renal anemia to rehabilitation outcome, specifically length of stay and discharge destiny in these patients. Retrospective chart review n = 62 Cancer patients admitted to the acute inpatient rehabilitation unit. Demographics not given BUN/Cr ratio ≥ 20 (pre-renal anemia) 1. Pre-renal anemia prevalence 2. Length of rehabilitation stay of pre-renal anemia group compared with non-pre-renal anemia group 3. Discharge destiny of pre-renal anemia group compared with non-pre-renal anemia group Patients classified into two groups: The pre-renal anemia group (n = 27) and the non-pre-renal anemia group (n = 35). Secondary analyses of collected data: - Demographics - Laboratory data - Length of stay - Discharge destiny Pre-renal anemia prevalence = 44% (n = 27/62) No significant association between pre-renal anemia on length of rehabilitation stay or discharge destiny.

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Design</th>
<th>Participants</th>
<th>Exclusions</th>
<th>Dehydration Definition</th>
<th>Outcome Measure</th>
<th>Methods</th>
<th>Appraisal: Total Score</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruera et al.</td>
<td>To determine the effect of clinically assisted hydration (CAH) on overall symptom control in terminally ill cancer patients with dehydration.</td>
<td>Randomized, controlled, double-blind trial</td>
<td>n = 51</td>
<td>NR: Sample size calculation 54 per group</td>
<td>Patient’s refusal to participate; the presence of severe dehydration, defined as a decreased systolic blood pressure of 30 mm Hg or lower from the patient’s baseline value; low perfusion of the limbs; no urine output for 12 h or longer; a decreased level of consciousness; or evidence of severe renal failure or bilateral hydropneumothorax.</td>
<td>Oral intake ≤ 1000 mL/d.</td>
<td></td>
<td>32</td>
<td>The administration of artificial fluids improved sedation and myoclonus in the intervention group.</td>
</tr>
<tr>
<td>Guo et al.</td>
<td>To determine the prevalence of pre-renal anemia in a cancer rehabilitation patient population. To evaluate the relationship of pre-renal anemia to rehabilitation outcome, specifically length of stay and discharge destiny in these patients.</td>
<td>Retrospective chart review</td>
<td>n = 8</td>
<td></td>
<td>Patients considered to have renal insufficiency.</td>
<td>BUN/Cr ratio ≥ 20 (pre-renal anemia)</td>
<td></td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>
### Waller et al. 56

**Are patients with cancer dehydrated when close to death?**

Does the provision of IV fluids influence the state of hydration of such patients or their level of consciousness?

**Cross-sectional survey**

- **n = 68** Hospice inpatients:
  - Terminal cancer
  - Laboratory tests done within 48 h of death (patients selected after death)

**Demographics not given**

**Number and details not given.**

**Elevated sodium, specific cutoff was not defined**

**Comparison of biochemical measurements and alertness scale measurements between groups.**

- **26** 87% (n = 59/68) of Patients classified as dehydrated.
- State of consciousness correlated inversely with serum sodium and urine osmolality.
- Patients receiving IV fluids were not better hydrated than those without IV therapy.
- State of consciousness was not improved for those hydrated compared with those without IV therapy.

### Burge57

**To determine the severity and distribution of symptoms associated with dehydration in inpatient palliative care patients.**

**To determine the association between these objective measures of dehydration.**

**Cross-sectional survey**

- **n = 52** PCU patients:
  - Age ≥18 y
  - Advanced cancer
  - Prognosis ≤6 wk
  - Ability to speak English or French
  - Ability to understand, consent to, and take part in study.

**Mean age = 64.4 y Male/female = 28/26 27% Died within 2 wk of study.**

**Dehydration not defined**

**Visual analogue scale (VAS) score for following symptoms:**

- Thirst
- Pain
- Dry mouth
- Nausea
- Fatigue
- Pleasure to drink

**Cross-sectional survey of palliative care inpatients across two hospitals.**

**Associations between symptoms and predictor variables (fluid intake, plasma osmolality, sodium, and urea).**

- **36** No association between severity of symptoms and fluid intake.
- No association between biochemical measures and thirst.
- Fatigue, dry mouth, and thirst are highly prevalent.

### Cerchietti et al. 9

**To assess the usefulness of hypodermoclysis hydration in the relief of thirst, chronic nausea, and delirium.**

**Randomized controlled trial**

- **n = 42** NR sample size = 50 Terminal stage patients with advanced cancer with one or more of the following:
  - Thirst
  - Chronic nausea or delirium
  - Dehydration diagnosed on physical examination (with or without renal failure)
  - Inability to maintain adequate water intake ≥50 mL/d

**Mean age = 55.8 y (intervention), 51.7 y (control) Number not given**

**Dehydration diagnosed on physical examination (with or without renal failure) Number not given**

**VAS for following symptoms:**

- Thirst
- Chronic nausea
- Delirium
- MMSE

**Twenty patients received 1000 mL 5% dextrose in water with addition of 140 mEq/L sodium chloride per day; at an infusion rate of 42 mL/h via the subcutaneous route. Twenty-two received no fluids.**

**VAS scores and MMSE used to compare hydrated and nonhydrated groups.**

- **28** Both groups showed significant and equal improvements in relief of thirst and nausea at 24 h, but this improvement was only maintained in the hydration group at 48 h. Delirium did not improve significantly in either group.

### Ellershaw et al. 54

**To investigate the relationship that respiratory tract secretions, thirst, and dry mouth have with level of dehydration.**

**Prospective cohort**

- **n = 82** Palliative care inpatients:
  - Advanced cancer
  - Dying and taking just sips of fluid or unable

**Patients were excluded if a doctor or nurse involved in the care of the patient felt that it was inappropriate for**

**Dehydration definition based on the presence of one or more of the following:**

- Self-reported symptoms (dry mouth and thirst) by patient
- Clinical assessment of respiratory tract secretions

**Based on dehydration definitions: 61 patients defined biochemically dehydrated, 21 not biochemically dehydrated.**

- **34** No statistically significant relationship between respiratory tract secretions, dry mouth, thirst, and

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
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<th>Participants</th>
<th>Exclusions</th>
<th>Dehydration Definition</th>
<th>Outcome Measure</th>
<th>Methods</th>
<th>Appraisal Total Score</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Morita et al. | To identify the association between sensation of thirst in hospice inpatients and various medical factors, especially dehydration. | Cross-sectional study     | n = 98 Patients with advanced cancer surviving at least 3 d, receiving palliative care at centers in Quebec and Ontario as part of a clinical trial for the prevention of delirium. | Age ≥18 y or older, Diagnosis of incurable advanced cancer, Physicians’ estimate of 6 mo life expectancy or less. | Two definitions used: 1. Atrial natriuretic peptide (ANP) >15 pg/mL. 2. Definition of Ellershaw et al.’s definition. | Biochemical definitions dehydrated. Comparison made between groups.       | - Serum osmolality >295 mOsmol/kg  
- Creatinine ≥130 μmol/L  
- Urea ≥12 mmol/L. | 32                    | No significant correlations observed between the VAS score for thirst and biochemical measures based on the Ellershaw definition. Dehydration defined by ANP level >15 pg/mL showed severity of thirst to be significantly associated with:  
- Hyperosmolality >300 mosmol/kg  
- Gastrointestinal cancer  
- Survival  
- Performance status  
- Oral intake  
- Vomiting  
- stomatitis  
- Mouth breathing and opioids potential causes of severe thirst as identified from retrospective chart review. Patients classified into six different groups based on presence/absence and course of delirium. Hydration was not predictive of delirium or group membership. |
| Galanakis et al. | To estimate the extent to which hydration and related risk factors influence the course of delirium over time. | Retrospective analysis of clinical trial data | n = 1125 Patients with advanced cancer surviving at least 3 d, receiving palliative care at centers in Quebec and Ontario as part of a clinical trial for the prevention of delirium. | Data unavailable. | Dehydration not defined. Relationship of hydration risk factors to delirium groups. Details of measures unavailable. | Data extracted from a clinical trial database. Group-based trajectory modeling and multivariate linear regression were used to identify subgroups of individuals with similar delirium trajectories during the first 30 d of admission and to determine what factors influence membership to these trajectories | 22                    | No significant correlations observed between the VAS score for thirst and biochemical measures based on the Ellershaw definition. Dehydration defined by ANP level >15 pg/mL showed severity of thirst to be significantly associated with:  
- Hyperosmolality >300 mosmol/kg  
- Gastrointestinal cancer  
- Survival  
- Performance status  
- Oral intake  
- Vomiting  
- stomatitis  
- Mouth breathing and opioids potential causes of severe thirst as identified from retrospective chart review. Patients classified into six different groups based on presence/absence and course of delirium. Hydration was not predictive of delirium or group membership. |
Yamaguchi et al. 61 To clarify the longitudinal changes in patient-reported global quality of life (QoL), observational discomfort, symptoms, and fluid retention signs in patients with advanced cancer receiving guideline-based parenteral hydration therapy.

Prospective, observational study

- Age > 20 y
- Incurable abdominal malignancy
- Severely reduced oral intake (<100 kcal/d and 10 mL/d)
- Available for follow-up
- Hepatic, prostate, or oesophageal malignancy
- Renal (creatinine > 2 mg/dL)
- Heart (NYHA classification > II), or liver failure (total bilirubin > 2 mg/dL) unrelated to malignancy
- Liver cirrhosis, nephrotic syndrome, or protein-losing enteropathy of any etiology
- Intra-abdominal shunt for ascites
- Hypothyroidism, adrenal insufficiency, MAIH requiring intervention
- Cognitive impairment
- Antitumor therapy (surgical, radiological, or chemotherapy) within 2 wk before study
- Use of artificial enteral nutrition

Patients completed questionnaires weekly (Weeks 1–4) and then every 2 wk (up until Week 12 or death). Patients received CAH according to national Japanese guidelines. CAH reduced to < 1 L/d in patients with fluid retention signs.

Patients grouped as low volume (<1 L/d) and high volume (>1 L/d).

Dehydration not defined

Nakajima 63 To explore the influences of hydration volume toward the symptoms during the last 3 wk of life in these patients.

Prospective, observational study

- Number not given

Degree of dehydration defined on basis of three physical findings

Analyses of data collected:

Patients classified into two groups; the hydration group (n = 32) who received ≥ 1 L or more of artificial hydration per day both 1 and 3 wk before death, and the nonhydration group (n = 45) who did not.

The percentages of patients with deterioration in dehydration score in the last 3 wk were significantly higher in the nonhydration group than in the hydration group (55% vs. 13%; P = 0.027).

Significantly higher fluid retention symptoms reported in the hydration group compared with the nonhydration group: edema (57% vs. 35%; P = 0.040), ascites (35% vs. 14%; P = 0.057) and bronchial secretion (44% vs. 19%; P = 0.036).

No significant differences in the degree of pleural effusion and delirium.

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
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<th>Appraisal Total Score</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musgrave et al.62</td>
<td>To evaluate the effects of IV fluids in a group of dying patients.</td>
<td>Cross-sectional study</td>
<td>$n=19$</td>
<td>Inpatients on adult oncology unit - Terminally ill - Receiving IV fluids - Prognosis of $\leq 10$ d Demographics not given.</td>
<td>Dehydration not defined</td>
<td>Structured questionnaire developed by the researchers. Questionnaire was reviewed for content validity by an oncologist, two specialists in oncology nursing, and two statisticians.</td>
<td>Patients asked to complete a questionnaire recording severity of thirst. Serum biochemistry and fluid intake and output volumes recorded. Comparisons made between variables.</td>
<td>24</td>
<td>95% ($n=18/19$) of Patients reported thirst. No association between level of thirst with the amount of IV fluids received, BUN, and sodium levels. Little association between fluid retention signs and volume of fluid received.</td>
</tr>
<tr>
<td>Davis et al.15</td>
<td>To determine whether bioelectrical impedance analysis (BIA) correlates with hydration changes during CAH and to determine if these changes were of prognostic importance.</td>
<td>Prospective observational study</td>
<td>$n=50$</td>
<td>Inpatient PCU: - Acute cancer - Undergoing continuous hydration - Able to give consent Mean age $= 63$ y Male/female $= 30/20$</td>
<td>Dehydration not defined</td>
<td>Phase angle</td>
<td>Patients underwent BIA measurements for 3 consecutive days. Laboratory studies, patient weight and vital signs recorded. Patient survival calculated.</td>
<td>29</td>
<td>Higher phase angle before hydration predicts longer survival. Increase in phase angles during hydration predicted poorer survival and pre-existing intracellular dehydration, cachexia, or poor membrane function.</td>
</tr>
<tr>
<td>Crawford et al.78</td>
<td>To investigate whether bioimpedance spectroscopy (BIS) has the potential to improve prognostication in an outpatient clinic for patients with cancer receiving palliative care.</td>
<td>Observational</td>
<td>$n=84$</td>
<td>Outpatient oncology and palliative care clinics: - Advanced cancer - Pharynx in English - Age $\leq 18$ y - Judged by their primary medical specialist to be in the palliative phase of their illness - No severe cognitive impairment Mean age $= 65.9$ y Male/female = not given</td>
<td>Dehydration not defined</td>
<td>BIS measures and survival time</td>
<td>Survival time and BIS measurements of basal metabolic rate and measurement of 11 body composition parameters (extracellular fluid (ECF), intracellular fluid (ICF), ECF/ICF ratio, fluid in trunk and arm and leg, protein mass, mineral mass, and percent of body fat) were recorded.</td>
<td>36</td>
<td>Metabolic rate and accumulation of body fluid are indicators of poor prognosis in palliative cancer patients.</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association Functional Classification; SIADH = symptom of inappropriate antidiuretic hormone secretion.
Dear Professor Varro,

Study title: Hydration in advanced cancer patients: the testing of a new assessment method

REC reference: 12/WA/0200
IRAS reference: 48056
Protocol number: UoL000863

The REC gave a favourable ethical opinion to this study on 23 July 2012. Notification(s) have been received from local assessor(s), following site-specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s) and investigator(s) listed below:

<table>
<thead>
<tr>
<th>Research Site</th>
<th>Principal Investigator / Local Collaborator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marie Curie Hospice Liverpool</td>
<td>Prof John Ellershaw</td>
</tr>
</tbody>
</table>

The favourable opinion is subject to management permission or approval being obtained from the host organisation prior to the start of the study at the site concerned.

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

12/WA/0200 Please quote this number on all correspondence

Yours sincerely

Mr Derek James Crawford
Chair
E-mail: rossela.roberts@wales.nhs.uk
Copy to: Sponsor / R&D Office:
Mrs Lindsay Carter
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Research Support Office,
2nd Floor, Block D, Waterhouse Bld,
3 Brownlow Street
Liverpool
L69 3GL  lindsay.carter@liverpool.ac.uk

Co-Investigator:
Dr Amarachukwu Nwosu
Academic Research Fellow in Palliative Medicine
Marie Curie Palliative Care Institute Liverpool (MCPCIL)
Dept of Molecular & Clinical Cancer Medicine, University of Liverpool
Cancer Research Centre
200 London Rd, Liverpool
L69 3BX  anwosu@liv.ac.uk
Dear Professor Varro,

Study title: Hydration in advanced cancer patients: the testing of a new assessment method
REC reference: 12/WA/0200
IRAS reference: 48056
Protocol number: UoL000863

The Research Ethics Committee reviewed the above application at the meeting held on 19 July 2012. The Committee wishes to thank the Co-Investigator, Dr Amarachuckwu Nwosu, for attending to discuss the study.

Ethical opinion

Ethical issues raised by the Committee in private discussion, together with responses given by Dr Nwosu when invited into the meeting

Scientific design and statistical analysis; conduct of the study; patient involvement in design
The Committee noted that this is a comparison of a CE marked device with a standard technique; the purpose of this clinical investigation is to demonstrate safety and performance of the device, not efficacy and therefore a smaller sample size is acceptable for this ‘proof of concept’ study.
The Committee raised a query in relation to the outcome measures.
The Co-Investigator clarified that the aim is to generate reference data which is population specific; survival data is required as hydration markers have been used for survival prognosis: it is hoped to identify whether readings using Bioelectrical Impedance Vector Analysis techniques have the same predictive value.
The Committee requested a clarification of the level of patient involvement in the design of the study, as the Project Management Team and the Project Steering Group are comprised solely of experts and the Project Advisory Group lists only two lay members.

23 July 2012
The Co-Investigator clarified that the project is based on feedback on previous work by patients and their families, who highlighted that they would like to see more work done on hydration; the Marie Curie Advisory Board have significant PPI representation and albeit they have not had as much input into this project the lay officer has offered to provide advice on the study.

The Committee suggested that the dissemination of results should not be restricted to web-based applications, and that other methods (such as leaflets in GP surgeries) could be considered.

**Independent review**

The Committee discussed the review of the project by the Chief Investigator’s institution and the level of external peer-review. It was noted that one of the reviewers suggested that avoiding the recruitment of very ill patients means missing the most valuable information; Dr Nwosu clarified that this was discussed at length in the project team and it was recognised that very important data could be obtained from patients in the dying phase; the team concluded that it was more appropriate to conduct the pilot study in patients able to give consent and able to participate in the assessments (such as visual assessment scores).

**Recruitment arrangements; fair participant selection.**

The Committee was satisfied that the participators will be recruited fairly and the selection of potential participants has taken into account their clinical care; there are no incentives and payments made to participants. The applicants went to considerable length to avoid a potential conflict of interest between the research team and the clinical care team and to avoid coercion; Adequate insurance and indemnity/compensation arrangements are in place. The Committee queried whether the researcher who is not part of the clinical team has legitimate access to the list of admissions required to identify potential participants; the Co-Investigator clarified his current role is that of a researcher not a clinician. The Admissions Coordinator runs admissions meetings in the morning; these are attended by all doctors and Co-Investigator is planning to attend in order to identify potential participants, whom he could approach during the day. The Committee advised that – as the Co-Investigator is not part of the clinical care team - it is preferable that the PI for the site (Professor Ellershaw), would identify eligible patients and introduce Dr Nwosu to potential participants.

**Care and protection of research participants; respect for participants’ welfare & dignity; data protection and participants’ confidentiality**

The Committee discussed where and for how long will data be stored, whether information about subjects be appropriately handled, and clarified who will have access to the data. The Committee queried the answer to question A36 of the REC application form which mentions ‘electronic transfer of data’. Dr Nwosu clarified that the analyser can send the results /readings directly to the computer in a pseudo-anonymised format, coded by identifier rather than by any patient identifiable information.

**Suitability of the applicant and facilities**

The Committee discussed the suitability of the applicant and concluded that the Chief Investigator is excellently qualified to carry out this research. The Committee discussed the requirement for Site-Specific Assessment for the non-NHS sites involved (hospices) and concluded that the study can be considered SSA exempt as it involves no clinical interventions and all study procedures at these sites will be undertaken by the Chief Investigator’s team. The REC was satisfied that the risk to participants is likely to be negligible and the study procedures will not significantly interfere with participant’s freedom of action or privacy or be unduly invasive or restrictive. However, it was noted that the research team have sent a request for a Site Specific Assessment to the Liverpool REC and it was decided that the conditions of approval should list that activities at non-NHS sites should be initiated only after the receipt of the notification of “No Objection”. No further ethical issues were raised.

The Chairman thanked Dr Nwosu for attending to speak to this submission and gave an opportunity to the applicant to ask questions. Dr Nwosu did not raise any issues.
On the basis of the information provided, the Committee was satisfied with the following aspects of the research:

- Social or scientific value; purpose and need
- Scientific design and statistical analysis; conduct of the study; patient involvement in design
- Independent review
- Fair participant selection
- Risks, burdens and benefits to the subject; favourable risk benefit ratio; redress
- Care and protection of research participants; respect for participants' welfare & dignity; data protection & participant’s confidentiality
- Informed Consent process; adequacy and completeness of Participant Information
- Other study procedures (e.g. scans, tissue samples)
- Other safety issues pertaining to the medical device
- Suitability of the Applicant and Supporting Staff

The Committee identified issues with the following aspects of the research:

- Recruitment arrangements

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

Non NHS sites
The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission (“R&D approval”) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.
The favourable opinion is subject to the following conditions being met prior to the start of the study:

1. As the researcher is not part of the clinical team he has no legitimate access to the list of admissions required to identify potential participants; the Committee requested that the recruitment arrangements are clarified in the protocol.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering Letter</td>
<td></td>
<td>04 July 2012</td>
</tr>
<tr>
<td>REC application (48056/341321/1/170)</td>
<td></td>
<td>09 July 2012</td>
</tr>
<tr>
<td>Protocol</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Other: Appendix 1: Bioelectrical impedance analysis testing procedure</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Other: Appendix 2: Bioelectrical impedance vector analysis and RXc graph with 95%, 75% and 50% tolerance ellipses</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Other: Appendix 3: Bioelectrical impedance vector analysis and RXc graph: graphical representation of hydration change</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Summary/Synopsis Appendix 4: Consent Process flowchart</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Participant Information Sheet: Appendix 5: PIS part 1</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Participant Information Sheet: Appendix 6: PIS part 2</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Other: Appendix 7: Screening questions for study entry</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Other: Appendix 8: Assessment Schedule</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Questionnaire: Appendix 9: Demographic details collection sheet</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Questionnaire: Appendix 10: Hydration questionnaire Burge 1993</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Questionnaire: Appendix 11: Hydration questionnaire Morita 2006</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Other: Appendix 12: Blood results template</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary/Synopsis Appendix 13: Flowchart of research protocol</td>
<td>1</td>
<td>01/06/2012</td>
</tr>
<tr>
<td>Referees or other scientific critique report Appendix 14: Peer-reviewer comments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referees or other scientific critique report Appendix 15: Response to Peer-reviewer comments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advertisement</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Participant Consent Form</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>GP/Consultant Information Sheets</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Investigator CV</td>
<td></td>
<td>27 June 2012</td>
</tr>
<tr>
<td>Letter from Sponsor: LCTU trial adoption</td>
<td></td>
<td>30 April 2012</td>
</tr>
<tr>
<td>Letter from Sponsor: confirmation of sponsorship</td>
<td></td>
<td>07 June 2012</td>
</tr>
<tr>
<td>Letter from Statistician</td>
<td></td>
<td>22 February 2012</td>
</tr>
<tr>
<td>Letter of invitation to participant</td>
<td>1</td>
<td>01 June 2012</td>
</tr>
<tr>
<td>Other: Letter form funder</td>
<td></td>
<td>28 June 2012</td>
</tr>
<tr>
<td>Instructions for use of medical device: EFG ElectroFluidGraph User Manual</td>
<td></td>
<td>rev 2 07/08</td>
</tr>
</tbody>
</table>
Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.
No conflicts of interest were declared in relation to this application.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/WA/0200 Please quote this number on all correspondence

Yours sincerely

Mr Derek James Crawford
Chair

E-mail: rossela.roberts@wales.nhs.uk

Enclosure: List of names and professions of members who were present at the meeting and those who submitted written comments

“After ethical review – guidance for researchers”
Copy to: 

Sponsor / R&D Office:
Mrs Lindsay Carter
University of Liverpool
Research Support Office,
2nd Floor, Block D, Waterhouse Bld,
3 Brownlow Street
Liverpool
L69 3GL  lindsay.carter@liverpool.ac.uk

Co-Investigator:
Dr Amarachukwu Nwosu
Academic Research Fellow in Palliative Medicine
Marie Curie Palliative Care Institute Liverpool (MCPCIL)
Dept of Molecular & Clinical Cancer Medicine, University of Liverpool
Cancer Research Centre
200 London Rd, Liverpool
L69 3BX  anwosu@liv.ac.uk
## North Wales Research Ethics Committee - West

### Attendance at Committee meeting on 19 July 2012

#### Committee Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Karen Addy</td>
<td>Clinical Psychologist</td>
<td>Expert</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr. Swapna Alexander</td>
<td>Consultant Physician</td>
<td>Expert</td>
<td>Yes</td>
</tr>
<tr>
<td>Ms Valerie Barcoft</td>
<td>Volunteer Worker</td>
<td>Lay +</td>
<td>Yes</td>
</tr>
<tr>
<td>Mrs. Kathryn Chester</td>
<td>Research Nurse</td>
<td>Expert</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr. Christine Clark</td>
<td>Consultant Obstetrician &amp; Gynaecologist</td>
<td>Expert</td>
<td>Yes</td>
</tr>
<tr>
<td>Mr. Derek James Crawford</td>
<td>Consultant Surgeon (Chairman)</td>
<td>Expert</td>
<td>Yes</td>
</tr>
<tr>
<td>Mrs. Gwen Dale-Jones</td>
<td>Retired Personal Assistant</td>
<td>Lay +</td>
<td>Yes</td>
</tr>
<tr>
<td>Mr. Hywel Lloyd Davies</td>
<td>Solicitor (Alternate Vice-Chairman)</td>
<td>Lay +</td>
<td>No</td>
</tr>
<tr>
<td>Mr. Ron Evans</td>
<td>Retired Teacher</td>
<td>Lay +</td>
<td>Yes</td>
</tr>
<tr>
<td>Ms. Gillian Jones</td>
<td>Student</td>
<td>Lay +</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr. Mark Lord</td>
<td>Consultant Pathologist</td>
<td>Expert</td>
<td>Yes</td>
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<tr>
<td>Dr. Neil McKenzie</td>
<td>Retired Physicist</td>
<td>Lay +</td>
<td>Yes</td>
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<tr>
<td>Mr. Paramasivam Sathyamoorthy</td>
<td>Consultant Orthopaedic Surgeon</td>
<td>Expert</td>
<td>Yes</td>
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<tr>
<td>Dr. Thanthullu Vasu</td>
<td>Consultant Anaesthetist</td>
<td>Expert</td>
<td>No</td>
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<tr>
<td>Mr. Christopher John Whitaker</td>
<td>Statistician</td>
<td>Expert</td>
<td>Yes</td>
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<tr>
<td>Dr. Philip Wayman White</td>
<td>General Practitioner (Vice-Chairman)</td>
<td>Expert</td>
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#### Deputy Members

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<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
<th>Present</th>
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<tbody>
<tr>
<td>Mrs. Rebecca Burns</td>
<td>Research Nurse (deputy to Mrs. Chester)</td>
<td>Expert</td>
<td>No</td>
</tr>
<tr>
<td>Dr. Michael Cronin</td>
<td>Consultant Paediatrician (deputy to Dr. Clark)</td>
<td>Expert</td>
<td>No</td>
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</tbody>
</table>

#### In attendance

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Rossela Roberts</td>
<td>Committee Coordinator</td>
</tr>
</tbody>
</table>
REFERENCES

7. Geoffrey Hanks Professor of Palliative Medicine UoB, UK Nathan I. Cherny Norman Levan Chair of Humanistic Medicine, Director CP, Palliative Medicine DoO, Shaare Zedek Medical Center, Jerusalem, Israel Nicholas A. Christakis Professor, Department of Health Care Policy, Harvard Medical School, Professor DoS, Harvard Faculty of Arts, Sciences, Attending Physician DoM, Mt. Auburn Hospital, Harvard Medical School, Boston, USA Marie Fallon St Columba’s Hospice Chair of Palliative Medicine, University of Edinburgh, UK Stein Kaasa Palliative Medicine Unit, Trondheim University Hospital, Norway Russell K. Portenoy Chairman, Gerald J., et al. *Oxford Textbook of Palliative Medicine*. New York, NY: ‘Oxford University Press’.

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