Systematic Review – the Effectiveness, Efficacy and Safety of Giraffe OmniBeds

by

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Abstract

Extremely low birth weight (ELBW) preterm infants face many risk factors. The Giraffe OmniBed is a hybrid incubator-radiant warmer designed to treat complications of prematurity while minimizing environmental risks infants face when treated and transported using other interventions.

Does the Giraffe OmniBed improve effectiveness, efficacy and safety outcomes for ELBW preterm infants? A systematic review of literature was conducted to answer the question. Two observational studies were identified for inclusion. While very low quality evidence suggests that the Giraffe OmniBed improves thermal stability, growth and skin maturity for ELBW preterm infants, it cannot be said, with confidence, until further research is done.

Scarcity of evidence is a problem shared within the medical device industry, with the regulation of devices influencing evidence generation. Health care resources are finite. Informed decisions around the allocation of resources and thorough assessment of medical devices are crucial components of sustainable high quality healthcare.

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List of Abbreviations

AdvaMed – Advanced Medical Technology Association
AHRQ - Agency for Healthcare Research and Quality
BPD - bronchopulmonary dysplasia
BW - bodyweight
CADTH – Canadian Agency for Drugs and Technologies in Health
CDR – Common Drug Review
CDRH - Centre for Devices and Radiological Health
CE - Conformité Européenne
CI – conventional incubator
CIHI - Canadian Institute for Health Information
CMDR - Canadian medical devices regulations
CMS - The Centre for Medicare and Medicade Services
C-section – caesarean section
EBM – evidence based medicine
ELBW – extremely low birthweight
EPC – Evidence-based Practice Centre
FDA – U.S. Food and Drug Administration
FD&C - Food, Drug and Cosmetic Act
g – grams
GA – gestational age
GE – General Electric
GHTF – Global Harmonization Task Force
GV – growth velocity
GW – gestational weeks
h – hour
HDE - humanitarian device exemption
HHS - the US Department of Health and Human Services
HI – hybrid incubator
HQO – Health Quality Ontario
HTA – health technology assessment
HTAi - Health Technology Assessment International
ICU – intensive care unit
IEC – International Electrotechnical Commision
IHE – Institute of Health Economics in Alberta
IMDRF - The International Medical Device Regulators Forum
INAHTA - International Network of Agencies for Health Technology Assessment
INESSS - Institut National d'excellence en Santé et en Services Sociaux
ISO – International Organization of Standardization

ISPOR - International Society for Pharmacoeconomics and Outcomes Research
IVH – intraventricular hemorrhage
IWL – insensible water loss
K^+ - potassium
kg – kilogram
KPRA – Kaiser Permenente Research Affiliates
MDD - medical device directive
MDEL - medical device establishment license
MDIC - Medical Device Innovation Consortium
MDL - medical device license
MDR – Medical Device Regulations - UK
mEq/L – milliequivalent of solute per litre
MHRA - The Medicines and Healthcare Products Regulatory Agency
ml – milliliters
MOU – memorandum of understanding
n - number
Na^+ - sodium
NEC - necrotizing enterocolitis
NHS – National Health Service – UK
NICE - The National Institute for Health and Care Excellence
NICU – neonatal intensive care unit
NIHR - The National Institute for Health Research
NIHR HTA – The National Institute for Health Research Health Technology Assessment Programme
NOS – Newcastle-Ottawa Scale
NR – not reported
OCCI – Ontario Case Costing Initiative
OTA - the Office of Technology Assessment
pCODR -Pan-Canadian Oncology Drug Review
pCPA - Pan-Canadian Pharmaceutical Alliance
PDA- patent ductus arteriosus
PICO - population, intervention, comparator, outcomes
PMA – premarket approval application
PND – post-natal day
RCT – randomized controlled trial
RWD – real-world data
SE – standard error
TAP – technology appraisal programme
TEWL – transepidermal water loss
TGA – Therapeutic Goods Act

TPD – medical device bureau of the therapeutic products directorate
U.K. –United Kingdom
U.S. –United States
VLBW – very low birthweight
WHO- The World Health Organization

1.0 Background

The Giraffe OmniBed is a hybrid medical device that combines a neonatal incubator and radiant warmer. It was designed to minimize environmental risks faced by vulnerable newborns when undergoing medical and nursing procedures throughout the first weeks of their lives by providing a stable microenvironment in which the newborn can thrive (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). This technology allows healthcare professionals to treat infants without moving them, thereby mitigating risk factors like thermal fluctuation and exposure to dust. The hybrid device is meant to replace the separate use of neonatal incubators and radiant warmers (General Electric, 2011).

While the Giraffe OmniBed is not the only hybrid medical device that combines a neonatal incubator and radiant warmer on the market today, it was the first. Other manufacturers have come out with similar devices, and in the United States, the Giraffe OmniBed has been identified as a predicate device by those manufacturers applying for 510(k) regulatory approval, as this process relies on proving substantial equivalence to another approved device for regulatory approval (US FDA, 2017). Internationally, medical device approval does not face the same rigorous process as other health technologies, like pharmaceutical drugs (Tarricone, Torbica, & Drummond, 2017). In high income countries, medical devices, like the Giraffe OmniBed, often replace existing technologies without a body of evidence that the new technology produces better health outcomes than the existing technologies. Decision-makers face many challenges when introducing a new device into their country, province, healthcare system, or organization (Conference Board of Canada, 2017). In understanding the efficacy, effectiveness, and safety of the Giraffe OmniBed, it is important to also understand how medical devices are regulated, evaluated through health technology assessment (HTA), and procured.

1.1 Health Technology Assessment and Regulation of Medical Devices

1.1.1 Innovation, Adoption and Diffusion of Health Technologies

Health technologies are complex interventions, that can take the form of drugs, devices, vaccines, or organizational, procedural and managerial systems developed to address a health issue and improve the quality of life of a patient (World Health Assembly, 2007; World Health Organization, 2011). These interventions are often comprised of many elements such as process, organizational and technological innovations (Institute of Health Economics Alberta Canada, 2015).

The need for new health technologies is often identified by either a healthcare professional or a scientist who works in the industry. Figure 1 shows a standard pathway of a health technology innovation. This simplified pathway shows that conception starts with identifying a medical need. Research and development carried out in consultation with clinical experts and engineers eventually leads to the creation of a new innovation that can only be diffused into society after clinical trials and regulatory approval (Oommen & Jatinder, 2010).

Adoption of a health technology is the discrete decision to either accept or reject the technology (Rye & Kimberly, 2007; Institute of Health Economics Alberta Canada, 2015). Implementation is the process of putting the decision to adopt into practice. Diffusion of a health technology is the process by which the technology is spread through specific channels by members of a social system over time (INESSS, 2015).

Adoption and diffusion of a health technology involves a diverse group of stakeholders. The process is influenced by the complexity and nature of the technology, perceptions of the adopters and the characteristics of the healthcare system. Diffusion is also influenced by the environment in which stakeholders are situated including the structure of an organization and its regulatory and financing systems (Chaudoir, Dugan, & Barr, 2013;

Institute of Health Economics Alberta Canada, 2015). Canada and other countries, with similar economic means, are considered to be high users of new technologies (Parker, Simpson, & Stevens, 2006). It is important that decision-makers make informed choices about which technologies are adopted and implemented in society as it is extremely difficult to reverse utilization of ineffective technologies.

1.1.2 Health technology assessment of medical devices

A medical device is an instrument, material, apparatus, machine or other article that can be used alone or in combination for the purposes of monitoring, prevention, investigation, diagnosis, treatment of illness or disease, or for modifying the function or structure of the anatomy of the body in order to address a health issue. It is further defined as a medical device to be one that addresses a health issue that cannot be addressed by immunological, pharmacological or metabolic means (World Health Organization, 2011; European Commission, 1993; Minister of Justice, 2017). A medical device is considered to be clinically effective when it produces its desired effect relative to the medical condition it was intended to address (World Health Organization, 2003).

A thriving medical innovation industry drives the health care system in developed countries such as Canada and the United States. 1n 2012 the global medical device market was valued at US$327.7 billion (CAD$385.6 billion as of January 1, 2012) and it is expected to reach US$342.9 billion (CAD$350.3 billion as of January 1, 2012) by 2021 (Trade and Development Canada, 2014; Lucintel, 2016; OANDA, 2017). In 2016, the Canadian medical device industry was valued at $USD 6.7 billion ($CAD 9.3 billion as of January 1, 2016) (OANDA, 2017; Government of Canada, 2017). There are approximately 1500 medical device firms employing approximately 35 000 people nationwide (Trade and Development Canada, 2014).

Over the last century significant progress has been made in the treatment of diseases and conditions that were previously death sentences. Much of this progress was due to the development of new cutting-edge medical devices. Advancements in medical

technologies, like the creation of hybrid neonatal incubator-radiant warmer, gives hope for a more efficient delivery of health care and, in turn, better patient outcomes. However, such advances usually come with a significant increase in health care expenditures (Oommen & Jatinder, 2010; Institute of Health Economics Alberta Canada, 2015).

Limited resources and ever increasing health care costs have resulted in a greater need to evaluate the effective use of resources. In theory, proven safety, efficacy, effectiveness and cost-effectiveness of a health technology could result in the implementation and diffusion of the technology into everyday practice. This is not always the case as the process of innovation, diffusion, adoption and implementation has proven to be complicated (Greenhaulgh, Robert, MacFarlene, Bate, & Kyriakidou, 2004; Kalkan, 2014). Several stakeholders and decision-makers are involved in this complicated process and now, more than ever, they require evidence-based information to help them make the best possible decision.

HTA is the multidisciplinary systematic process of evaluating available evidence on a health technology and providing that information to decision-makers (INESSS, 2015). It is a form of policy research that is intended to support decision making in an unbiased, transparent way. Depending on the policy that a HTA is created to inform, the framework can be adapted and different factors can be considered. Information on the safety, costs, and effects of a health technology can be assessed from various perspectives, including, social, ethical and economical (Conference Board of Canada, 2017). The process shares its principles with evidence-based medicine (EBM) and is considered to be a bridge between the academic world of research and the political world of decision-making (Battista R. N., 1996).

HTA agencies use frameworks to assess the value of health technologies in a reproducible way. Frameworks can vary among countries, provinces and agencies; however, the overarching principles are the same. A standard HTA report framework usually includes a systematic review of the available clinical literature (efficacy and

effectiveness) with a critical appraisal of the clinical evidence, an economic analysis, and a consideration of ethical, social and legal issues (Ludwig Boltzmann Institute, 2011). When a decision is being made on the allocation of health care resources, additional value parameters may be added to the framework. A value framework includes criteria that may differ between agencies due to political and cultural differences between jurisdictions. Many judgement calls are made throughout the value assessment process like selecting relevant endpoints and deciding which comparators should be used to determine the effectiveness of the health technology (Oortwijn W. , 2017)

Generally, decision-makers prioritize the uptake of technologies that reduce duplication and costs while improving safety and effectiveness outcomes. A thorough and transparent HTA report helps consolidate information for decision-makers so that they can make a well-informed choice (Chaudoir, Dugan, & Barr, 2013; Institute of Health Economics Alberta Canada, 2015)

A large component of HTA involves comparing clinical outcomes with the cost of interventions. While HTA is routinely applied to drugs and surgeries, it has proven to be more challenging for medical devices. Drummond et al. discussed many ways that economic evaluations and HTAs of medical devices differ from pharmaceutical evaluations. Due to frequent modifications, short life cycles, and associated learning curves of medical devices, there is rarely time to evaluate them in a randomized controlled trial (RCT). Additionally, it is almost impossible to conduct a blinded study when assessing a medical device (Drummond, Griffin, & Tarricone, 2009). Efficacy of a device depends on both the device itself and how it is used. Effectiveness findings can be impacted by the skill-level of the person operating the device which can change over time. Comparisons may be difficult between products because equivalent clinical evidence may not be available (Drummond, Griffin, & Tarricone, 2009). All of these considerations, among others, result in the necessity for a specialized approach when conducting an HTA of a medical device.

Economic evaluations can be used to inform decision-makers on prioritizations, reimbursement, and pricing. They strive to help decision-makers harness the benefits of a technology while getting value for money (Conference Board of Canada, 2017). An economic evaluation deals with both inputs and outputs (costs and consequences) of an intervention and concerns itself with choices. Choices are made on various criteria that can be both explicit and implicit (Drummond M. F., Sculpher, Torrance, O'Brien, & Stoddart, 2005).

A cost-effectiveness analysis (CEA) is an economic evaluation in which costs are related to a single, common effect that may differ in magnitude between alternative interventions. It is most useful when a decision-maker, operating within a concrete budget, is considering a limited range of options within a given field. It is measured in units such as life years gained or disability days and incremental cost effectiveness ratios (ICERs) (Drummond M. F., Sculpher, Torrance, O'Brien, & Stoddart, 2005). A Cost-Utility Analysis (CUA) is a form of CEA that involves a comparison of technologies and is measured in quality adjusted life years (QALYs) and ICERs.

In some high-income jurisdictions, after regulatory approval, medical devices are procured through centralized agencies at a regional or national level. Procurement at this level often relies on recommendations from HTAs. In other high-income jurisdictions, devices are procured and purchased at a local or hospital level. It is becoming increasingly more common for decision-makers at the hospital level to seek evidence-based recommendations from HTA producers (Martin, Polisena, Dendukuri, Rhainds, & Sampietro-Colom, 2016).

1.1.2.1 HTA Landscape in Canada

Canada has a single-payer public health system with universal health insurance. The federal government, through Health Canada, provides funding to provinces and territories as required by the Canada Health Act of 1984. There are five guiding principles within the Act that provinces and territories must respect in order to receive their funding. The

legislation states that the health system must be universal and governed by a public administration, portable across provinces, comprehensive, and allow for equity of access (Health Canada, 1984). As provinces and territories are primarily responsible for the delivery and administration of health services, they are also responsible for many decisions around allocation of funds (Battista, Cote, Hodge, & Husereau, 2009). As the public health system, Medicare, is funded by tax dollars, there is a lot of pressure from taxpayers to exercise fiscal responsibility with the money decision-makers have been given.

The HTA landscape in Canada is a mix of centralized and decentralized structures and processes that have significantly expanded in the past 25 years. The Canadian Agency for Drugs and Technologies in Health (CADTH) is Canada's national non-profit HTA agency that was created in 1989 in an effort to coordinate healthcare assessment at various levels of government in Canada. Their goal is to provide decision-makers with objective evidence to support and inform their choices on the use of health technologies (CADTH, 2017).

The evidence requirements by Health Canada in the regulation process of a medical device, or lack thereof, is often inadequate to conduct a thorough HTA of that device. The lack of evidence can lead to inconsistencies that exist between HTA reports on the same technology produced by various HTA agencies in Canada. This variation between agencies can result in inconsistent funding availability and patient access between provinces and territories (Ferrusi, Ames, Lim, & Goeree, 2009).

In an effort to better coordinate HTA initiatives, much of Canada's HTA efforts are overseen by CADTH. CADTH not only produces HTA reports, but also coordinates information for provinces and territories, particularly those that do not have HTA organizations of their own. Some smaller provinces and territories in Canada do not perform their own HTAs and in turn rely heavily on CADTH and other provinces (Conference Board of Canada, 2017). Quebec has a unique and independent HTA process with its own assessment agency, the Institut National d'excellence en Santé et en Services

Sociaux (INESSS), that reports to Quebec's Minister of Health and Social Services (Conference Board of Canada, 2017). Other provinces that have HTA agencies in place are British Columbia with the BC Health Technology Review, Alberta with the Alberta Health Technologies Decision Process through Alberta Health, the Institute of Health Economics (IHE) HTA units at the University of Alberta and the University of Calgary, and Health Quality Ontario (HQO) in Ontario. Ontario also has many academic HTA groups such as the Toronto Health Economics and Technology Assessment (THETA) Collaborative and the Programs for Assessment of Technologies in Health (PATH) Research Institute at St. Joseph's Healthcare Hamilton, affiliated with McMaster University (Conference Board of Canada, 2017).

The Pan Canadian HTA Collaborative is a national initiative that was formed in 2011 to share best practices, reduce duplication of HTA reports undertaken by agencies, facilitate information sharing between HTA agencies, and identify and participate in joint initiatives in the HTA of medical devices, procedures and diagnostics (Polisena, 2017). Membership includes CADTH, INESSS, IHE, and HQO among others. The collaboration acts as a forum for members to discuss and share information on HTA initiatives. The collaboration partnered with the U.K.'s National Institute for Health Research Centre for Reviews and Dissemination in an important initiative to create an international database. Together they developed an international database to provide researchers a vehicle through which topic repetition can be reduced and HTA efficiency can be increased worldwide. The database currently serves as a repository and search tool for HTA reports and materials produced by the 49 INAHTA members as well as 20 additional HTA organizations (Conference Board of Canada, 2017).

CADTH has a centralized review process to support the drug coverage decision-making of federal, provincial and territorial governments (with the exception of Quebec) through the Common Drug Review (CDR) or the Pan-Canadian Oncology Drug Review (pCODR). Drugs are chosen to be assessed through horizon scanning. Once Health Canada has approved a drug for use in Canada, the CDR and pCODR provide a list of recommendations for reimbursement (CADTH, 2017). Generic and brand name drugs

being reviewed for funding through the national review processes at the CDR and pCODR are considered for negotiation through the Pan-Canadian Pharmaceutical Alliance (pCPA). The pCPA is an initiative of the Premier's Council of the Federation that allows provinces and territories to work together to negotiate and achieve greater value of publicly funded drug programs (The Council of the Federations, 2018). While CADTH and Health Canada routinely communicate on priorities related to drugs, they do not always do so with medical devices (Menon & Stafinski, 2009).

For medical devices, some provinces use shared service organizations (SSOs) and group purchasing organizations (GPOs) to facilitate procurement of devices through group purchasing arrangements that are designed to leverage negotiating power with manufacturers. SSOs and GPOs consolidate efforts, reduce costs for health regions and provinces and are becoming increasingly more popular across the country (Husereau, Arshoff, Bhimani, & Allen, 2015).

Participation in the implementation of province-wide based HTA recommendations for medical devices is generally voluntary for hospitals and decision-makers, depending on the province (Husereau, Arshoff, Bhimani, & Allen, 2015). Medical devices chosen for assessment are identified by a hospital, environmental scanning or passive surveillance. HTA of medical devices at the province-level typically considers: disease burden and need for medical technology, comparative effectiveness, budget impact and/or total cost to the health system, cost-effectiveness, equity of access to the technology, implementation considerations, and access to the medical technology in other jurisdictions (Husereau, Arshoff, Bhimani, & Allen, 2015).

Unlike pharmaceuticals, no centralized process exists for the recommendation of medical devices in Canada. Local context can play a large role in device assessments with respect to funding, infrastructure, needs, and healthcare professional training (Polisena, 2017). Health Canada focuses on evidence about the safety and efficacy of a device whereas funders focus on procurement and use. While HTAs in Canada are carried out by national agencies, provincial bodies, and hospital-based units, reimbursement and

purchasing decisions for market-approved medical devices in Canada are, for the most part, made at the hospital level. Hospitals include the purchase of medical devices in their annual budget. In most provinces, budgets are allocated to hospitals by a regional health authority. (Martin, Polisena, Dendukuri, Rhainds, & Sampietro-Colom, 2016). Local HTA efforts are growing in Canada. Hospital-based HTA allows for more customized reports that include local data on costs, clinical practices, and usage. When making investment and disinvestment decision at a local-level, evidence on incremental benefit, risk, cost, and institutional impact must be weighed as well as the expected impact on health outcomes and the net costs to implement and manage a given technology (Martin, Polisena, Dendukuri, Rhainds, & Sampietro-Colom, 2016).

1.1.2.2 HTA Landscape in the United States

The Unites States has a unique and dynamic health care system. While the Affordable Care Act that mandates health care coverage for most of its citizens was enacted in 2010, the USA does not have universal coverage like the other countries highlighted in this report. The Act states that ensuring all Americans have health coverage is the shared responsibility of the government, employers and individuals (Smith & Medalia, 2015). The American system is a complex, hybrid system that has both public and private institutions delivering health care services. In 2014, according to a nationwide census, 89.4% of the USA's population had health insurance coverage. Medicare, Medicaid, and the military health plan are the publicly funded health insurance programs. Residents can receive coverage from more than one type of insurance at any given time. In 2014, while 10.4% of residents had no coverage, 66.0% were covered by a private health insurance plan and 36.0% were covered by a government-funded plan (Smith & Medalia, 2015). The Centre for Medicare and Medicaid Services (CMS) is the federal agency responsible for programming, financing, and implementation of publicly funded health services. The U.S. Department of Health and Human Services (HHS) is the principle agency involved in governing health care services. The FDA within the HHS is responsible for the regulation of food, pharmaceuticals, and medical devices among other products (U.S. Food & Drug Administration, 2017).

The complexity in the U.S. healthcare system has lends itself to a complex HTA landscape in the country. Many public and private agencies in the U.S. have HTA initiatives. HTA occurs at a federal level as well as a local, hospital-level (Sullivan, Watkins, & Sweet, 2009). The history of HTA, on a national scale, in the U.S. dates back to 1972 when the Office of Technology Assessment (OTA) was established and funded by the U.S. Congress, only to have funding withdrawn in 1995 over controversy about the content of their reports and political pressure (Sullivan, Watkins, & Sweet, 2009). The OTA is just one example of several federal HTA efforts that failed over the years (Luce & Singer Cohen, 2009). While there is quite a lot of information available on public HTA efforts, very little information is available on HTA processes undertaken by private insurers in the United States (Sullivan, Watkins, & Sweet, 2009).

Currently, the Agency for Healthcare Research and Quality (AHRQ) is the lead American federal agency working with the HHS that is responsible for improving the quality and safety of America's healthcare system (The Agency for Healthcare Research and Quality, 2014). Their goal is to produce evidence that will help foster higher quality, safer, more equitable, affordable, and accessible health care services in the U.S.. The AHRQ works with the HHS and other stakeholders to make sure that the evidence they produce is understood and used in the decision-making process. They have many programs, one of which is the Technology Assessment Program. Outputs by the AHRQ range from HTA reports to quality and disparity reports. Some of these outputs are completely created in-house while others rely on information from other agencies and centers (Agency for Healthcare Research and Quality, 2018).

Some of the reports that the AHRQ disseminates are produced by Evidence-based Practice Centers (EPC) that they support through their Effective Health Care Program. They currently fund 13 EPCs located across the United States and one in Alberta that produce technology assessment reports. Some of the centres are situated at academic centres like Johns Hopkins University while others are health research agencies that are closely affiliated with private insurance companies like the Kaiser Permanente Centre for

Health Research with locations in both Oregon and Hawaii (Agency for Healthcare Research and Quality, 2018).

National coverage decisions are the responsibility of the Coverage Division within the CMS (Luce & Singer Cohen, 2009). Technology assessments produced by the AHRQ are provided to the CMS to inform coverage decisions for Medicare (Agency for Healthcare Research and Quality, 2018). As with previously failed federal HTA initiatives, the funding of AHRQ's technology assessments is consistently challenged by political pressures. This pressure can result in unfavourable funding decisions made by the US Congress (Sullivan, Watkins, & Sweet, 2009). While the idea of evidence-based medicine, cost, and value and the need for evidence-based decision making are on the national agenda, there is a constant struggle to incorporate best practices it into healthcare decisions in the United States (Luce & Singer Cohen, 2009). Steps are continuously being taken, however, by various agencies in the U.S. government to coordinate efforts to provide health care users the best possible services. In June of 2010, for example, the FDA and the CMS signed a memorandum of understanding (MOU) that aimed to improve information sharing between agencies (Fronsdal, et al., 2012). The goal of this MOU is to expedite and improve access to better quality, evidence-based care through knowledge-sharing, including information related to innovative medical devices (U.S. Food & Drug Administration, 2010).

1.2.2.3 HTA Landscape in the United Kingdom

The United Kingdom includes Scotland, Northern Ireland, England and Wales. While this review focuses on England, the health systems and policies across all four countries are broadly similar. In England, the Department of Health and Social Care is responsible for the National Health System (NHS) and to create and oversee health and social service policy (Drummond & Banta, 2009; Drummond & Sorenson, 2009). The NHS was created in order to provide universal health coverage to all citizens as mandated in the National Health Services Act of 1946. Most financing for the NHS comes from public taxes, with contributions from the national insurance. The NHS Directive has several

guiding principles. Some of the principles include: Health services should be provided based on need rather than ability-to-pay, a wide range of high quality services should be provided and developed around the needs of individual patients and various patient populations, the NHS will strive to provide equity of access to health care services, and the NHS will protect patient confidentiality (Drummond & Sorenson, 2009; Wilson, 2010).

Health Technology Assessment has a long history in the United Kingdom with much of the focus being on drugs over the last 20 years (Mittendorf & Arvin-berod, 2016). The HTA program at the NHS started in 1993, however, international recognition for HTA efforts came in 1999 when the National Institute for Health and Care Excellence (NICE) was established (Drummond & Sorenson, 2009). NICE's mandate is to promote clinical excellence and to provide advice, through evidence, to decision-makers at the NHS. Their goal is to improve patient outcomes by providing advice and evidence-based guidance to clinicians and decision-makers (National Institue for Health and Care Excellence, 2017). While the U.K. has many HTA agencies at various governmental and non-governmental agencies in various jurisdictions, NICE is considered to be the main national HTA body for England (Drummond & Banta, 2009). While it officially only services England, agreements are also in place to provide Scotland, Wales and Northern Ireland with some of their products and services. In 2013, it became an Executive Non-Departmental Public Body, which is at arms-length from the NHS, designed largely to minimize political influence (National Institue for Health and Care Excellence, 2017).

NICE produces several outputs aside from HTA reports, such as, quality standards documents, public health guidelines, clinical guidelines, social care guidelines, and implementation tools. Since its inceptions, HTA programmes at NICE have included the technology appraisal programme (TAP), the clinical guidelines programme, the interventional procedures programme, public health guidance programme, the diagnostic assessment programme, medical technologies evaluation programme, the medical technologies guidance programme, and the highly-specialized technologies programme. In addition to these programmes, in accordance with the Health and Social Care Act of

2012, NICE began producing guidelines for Social Care as well (Brockis, Marsden, Cole, & Devlin, 2016).

As the primary function of NICE is to *appraise* technologies before providing recommendation to the NHS, some of the information they use on a health technology is *assessed* by another agency. The National Institute for Health Research (NIHR) produces independent research about the effectiveness, costs of healthcare treatments and tests, and the impact they have on patients and health care providers in the NHS (NIHR, 2018). The NIHR Health Technology Assessment Programme (NIHR HTA) at the NIHR, among other things, funds primary research and evidence syntheses on areas of interest to them and produces technology assessment reports (TARs) requested by NICE. Therefore, the NIHR HTA *assesses* technologies and acts as a bridge between policy-making and research by providing NICE with evidence-based reports to inform their technology appraisals, clinical guidelines, and other recommendations (Turner, Bhurke, & Cook, 2015).

The majority of recommendations produced by NICE are expected to be reflected in the budget of the NHS. The mandatory framework between NICE and the NHS says that funding must be made available within three months of their formal recommendation on drugs. Exceptions can occur because even if a health technology is proven cost-effective, the NHS may not have the funds to implement it (Brockis, Marsden, Cole, & Devlin, 2016; Conference Board of Canada, 2017). Cost thresholds used by the NHS include an ICER of £20 000 (CAD $ 35,441.30) and £30 000 (CAD $53,162.00) per QALY (OANDA, 2018). Overall, governments and HTA agencies lack consensus on which costs to include in an analysis, how they should be measured, and if a societal or health system approach should be taken (Culyer, et al., 2007; Conference Board of Canada, 2017).

For a medical device to be assessed by NICE, a manufacturer must fill out and submit a standard notification form (Mittendorf & Arvin-berod, 2016). The manufacturer must submit information on the target population, indication of use, comparators, one-time

costs, long-term costs, safety concerns, and any information they have on health outcomes, all supported by evidence. In addition, for medical device assessments, information on benefits to the health system, like patient days avoided, is required (Mittendorf & Arvin-berod, 2016). If the device meets all criteria required for an assessment, NICE compiles a briefing note and provides it to the medical technology advisory committee for them to decide if the device should be formally assessed. Providing information on the societal benefits of the device adds to the likelihood of the device being chosen for assessment. Once chosen, the committee then decides which program is the most appropriate to evaluate the device (Mittendorf & Arvin-berod, 2016) (Drummond & Sorenson, 2009). HTA reports are produced in-house as well as being contracted out to private HTA agencies. The approach followed by NICE has been shown to work, however, due to the lack of evidence available for many devices, like the Giraffe OmniBed, many evaluations are determined not to have enough evidence available for a robust and useful evaluation. As a result, the structure and frameworks used at NICE are still considered to be a work-in-progress (Drummond & Sorenson, 2009; Mittendorf & Arvin-berod, 2016).

In some countries, there are mechanisms in place to involve HTA in the regulatory process. There are benefits and challenges to incorporating HTA in regulation and reimbursement processes. Regulation requirements and the requirements needed to conduct an HTA are not well-aligned with the standard life-cycle of a medical device as most of these processes were originally created for pharmaceuticals and then adapted for medical devices (Ferrusi, Ames, Lim, & Goeree, 2009). Figure 2 shows the standard life-cycle for a medical device with respect to policy decisions. In the life-cycle of a drug, HTA generally happens before the drug gains market access. In the life-cycle of a medical device, a proper HTA can usually only be done after a device is already on the market. This is because researchers usually need more clinical evidence than is required by a regulatory agency, or undertaken by a manufacturer, for that device to be cleared and approved for the market (Ferrusi, Ames, Lim, & Goeree, 2009).

1.1.3. Regulation of Medical Devices

Regulatory approval is the process of authorizing a health technology with clearance for market access in a given jurisdiction (Henshall, Bayne, Frondsal, & Klemp, 2011). The regulation of medical devices is primarily concerned with ensuring patients have access to the highest quality safe and effective products available. This process focuses on patient safety and the technical functioning of the device (Henshall, Bayne, Frondsal, & Klemp, 2011). When properly executed, the regulation of medical devices can also ensure the safety of health care professionals and the community as a whole (World Health Organization, 2018). Such regulation is generally enforced at a national level with a government agency reporting directly to a Minister of Health, or equivalent government position (Fronsdal, et al., 2012). The role of a regulatory authority is to ensure manufacturers, device importers, and vendors all adhere to regulatory requirements. Regulatory requirements in Canada and many other high-income countries are based on a process of risk management and are separated into premarket regulation and post-market regulation (World Health Organization, 2003).

Medical Device Safety and Risk Assessment

All medical devices have a certain degree of risk associated with them. Unfortunately, in most cases it is impossible to predict and know all of the possible problems that can occur with any given device at any given time. Problems can occur or be detected after a long period of time on the market and may be unique to specific patients (World Health Organization, 2003).

The safety of a device is estimated by assessing the risk the device has of becoming a source of danger (hazard) that can cause harm and the likelihood that it will cause an adverse event (World Health Organization, 2018). Risk is assessed by evaluating the safety of the engineering design of a device and the experiences of healthcare professionals with that medical device. It is a complex process that can be influenced by

outside factors like patient characteristics, economic conditions, individual perceptions, and/or the politics of a country (World Health Organization, 2003).

Medical device safety is the shared responsibility of various stakeholders, including: manufacturers, importers, device users (healthcare professionals), patients, and governments. Cooperation and communication between and among all stakeholders are crucial in ensuring a medical device is used safely (Lamph, 2012). Regulations are generally enacted by an individual country's government. Manufacturers of medical devices must adhere to regulations of individual countries in order to gain access to the market of that country (Fronsdal, et al., 2012).

1.1.3.1 Brief Overview of Regulation of Medical Devices in Canada

In Canada, a manufacturer is defined "a person who sells a medical device under their own name, or under a trade-mark, design, trade name or other name or mark owned or controlled by the person, and who is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the device, or for assigning to it a purpose, whether those tasks are performed by that person or on their behalf" (Health Products and Food Branch Inspectorate, 2015).

Health Canada's Medical Device Bureau at the Therapeutic Products Directorate (TPD) evaluates and monitors the effectiveness, quality, and safety of medical devices nationwide. They strive to ensure good outcomes through a combination of pre-market review, post-approval surveillance and quality systems during the manufacturing process (Government of Canada, 2007). Regulation of medical devices in Canada is governed through the Food and Drugs Act of 1985 (Minister of Justice, 2017). The TPD enforces the Food and Drug Regulations and the Medical Devices Regulations (SOR/98-282) (CMDR) under the authority of the Food and Drugs Act (R.S.C., 1985, c. F-27) (World Health Organization, 2014). In-vitro diagnostic devices are defined and regulated differently than other medical devices and will not be included in the discussion of medical device regulation in this paper.

Pre-market Regulation in Canada

Pre-market regulation includes a product assessment, device classification, quality systems, and medical device licensing (World Health Organization, 2018).

Medical devices are classified into one of four categories, Class I, II, III, and IV based of level of risk. Factors that influence the class which a device is assigned to include: degree of invasiveness, amount of time in contact with a patient, the part of the body system that is affected, local versus systemic effects, level of hazard associated with energy transmission (devices powered by electricity), consequences if the device malfunctions or fails; Class I representing devices that carry the lowest risk and Class IV representing devices that have the highest risk (Government of Canada, 2007). The classification is reflected by the level of control applied by the TPD.

Post-market Regulation in Canada

Post-market regulatory activities include: licensing inspections, mandatory problem reporting, handling of complaints, maintaining distribution records, implant registration, and recall management (Minister of Justice, 2017).

1.1.3.2 International Regulation of Medical Devices

In the European Union (EU), as in Canada, classification of medical devices is predominantly rule-based according to their perceived potential risk. While Canada has four classes of devices, the EU has three levels with Class II devices being subdivided into IIa and IIb. The United States, with three classes of devices, mainly assesses risk from medical devices based on the recommendations from members of specialty panels (World Health Organization, 2003). There are significant differences, even in developed countries, in the way that medical devices are classified and regulated. In the United States, for example, manufacturers are issued a 510K Marketing Clearance or a Pre-

Market Approval letter from the Food and Drug Administration (FDA) (World Health Organization, 2003).

The International Medical Device Regulators Forum (IMDRF) is an organization that was formed in 2011 in an effort to harmonize medical device regulations worldwide. This collaboration of regulators has set out to try and accelerate international medical device regulatory harmonization and convergence. Their goal is to foster global convergence by leveraging resources in order to make safe and effective medical devices available globally (IMDRF, 2014). In 2017, in collaboration with IMDRF and its predecessor the Global Harmonization Task Force (GHTF), and the World Health Organization (WHO) published the Global Model Regulatory Framework for Medical Devices including In-vitro Diagnostic Medical Devices. The framework recommends guiding principles and harmonized definitions as well as specifying attributes of effective and efficient regulation for regulatory legislation (World Health Organization, 2017). Industry researchers and regulators are hopeful that if the regulation of devices was harmonized globally, and there was one central repository for all adverse events, the regulatory process could become more efficient, affording patients faster access to life-saving devices and manufacturers faster access to the market (World Health Organization, 2017). Canada, the United States, and the European Union are all members of the IMDRF along with six other countries (IMDRF, 2014).

Manufacturers of electronic medical devices, such as the General Electric, often have to meet device specification requirements outlined in technical documents published by the International Electrotechnical Commission (IEC). The IEC is an organization that produces consensus-based international standards and manages conformity assessment systems for electricity dependent products, systems and services. Organizations like the IEC and the ISO work to ensure that devices work efficiently and safely anywhere in the world (International Electrotechncal Commission , 2014). Canada, the United States and the United Kingdom are all full members of the IEC.

Regulatory bodies explicitly define requirements for the manufacturing process, distribution, and disposal of medical devices. Requirements for neonatal incubators are defined by international organizations like the IEC and ISO a well as national regulatory bodies. Any malfunction in the device can lead to life threatening injuries or even death of the infants being treated in them (Gurbeta, Izetbegović, & Badnjević-Cengić, 2018). Proper management of an incubator throughout its lifecycle is crucial to ensuring effective, safe and equal access to services to all patients. Electrical safety inspections and functional testing as defined by the IEC, with quality standards defined by the ISO, need to be periodically carried out to ensure safety and optimal performance of an incubator (Gurbeta, Izetbegović, & Badnjević-Cengić, 2018).

This review of the HTA and regulatory landscapes across Canada, the United States and the United Kingdom was done to demonstrate the differences and similarities in practices and requirements across jurisdictions. Medical device manufacturers and decision-makers both have crucial roles and responsibilities in ensuring patient safety when a device comes to market that differs across jurisdictions.

1.2 Preterm Birth in Canada

A preterm birth is defined as any baby born before thirty-seven completed weeks of gestation. Many preterm babies are born with a low birth weight. Low birth weight infants are defined as weighing less than 2500 g. This category is subdivided into Very Low Birth Weight (VLBW), weighing less than 1500 grams and extremely low birth weight (ELBW), weighing less than 1000 grams at birth with a corresponding gestational age of 23–28 weeks (Knobel, Holditch-Davis, & Schwartz, 2010). ELBW preterm infants are at increased risk of physical and cognitive disabilities, chronic health problems later in life and death (Laptook, Salhab, Bhaskar, & Network, 2007).

Preterm births can be medically indicated or can occur spontaneously for many different reasons. Socio-economic factors (income level, urban/ rural place of residence and accessibility to healthcare), maternal characteristics (age and ethnicity) and health history

(history of preterm birth, multiple births, physical and psychological stress, placental disorders and substance abuse) have also been known to influence labour and childbirth and are some of the most common reasons for preterm births in Canada (Iams, 2003; CIHI, 2009).

With the introduction of fertility treatments in the early 1970s, multiple births have been on the rise in developed countries. Increased use of fertility treatments, often due to women waiting until later in life to have children has contributed to an increase in multiple births in Canada. Multiple births can play a factor in preterm births. Preterm infants that are born in multiples can be restricted in their ability to grow due to limited nutrients and space available in the uterus. From 2006-2007 in Canada, 56.1% of all twins and 98% of higher multiples were born before 37 Gestational weeks (GW) (Goldenberg, Culhane, Iams, & Romero, 2008; CIHI, 2009).

The preterm birth rate in Canada has grown from approximately 6% in the early 1980s to approximately 8% in more recent years (CIHI, 2009; CIHI, 2016). From 2006-2007, the Canadian preterm birthrate was approximately 8%, or almost 29,000 births. Of these, 74% were born between 34 and 36 weeks, 11.7% were born between 32 and 33 weeks, and 14.3% were born less than 32 GW. Of all preterm births, 54.5% were low birth weight (CIHI, 2009). Over the last decade, the preterm rate has remained relatively stable. From 2015-2016 the preterm birthrate in Canadian hospitals was 7.9%. The rate for small gestational age (GA) singleton babies born from 2015 -2016 was 9.1% (CIHI, 2016). The rates varied between provinces and territories with a rate as low as 6.2% in Prince Edward Island and a rate as high as 11.1% in Nunavut. Ontario's rate was 8.0% (CIHI, 2016).

Preterm infants are at higher risk for morbidity and mortality than full-term infants and, in turn, account for a high percentage of the health care costs associated with newborns. Morbidity is defined as the incidence rate of disease in a specific population and mortality is the rate of death. The morbidity impact of prematurity is not limited to the

neonatal period of life. Morbidities can lead to physical and cognitive developmental impairments and learning disabilities that can come at a considerable cost to individuals, families, and society throughout their lifetimes (CIHI, 2009; Saigal & Doyle, 2008).

1.2.1 Preterm Birth as a Global Issue

Worldwide, every year, approximately 15 million babies are born preterm (birthrate of approximately 11.1%). To date, premature birth is the leading cause of death for newborn babies (WHO, 2012). In 2012, The World Health Organization (WHO) released a comprehensive report on preterm birth globally. The report was based on information from countries with reliable data that were collected from national registries, surveys and special studies (Blencowe, et al., 2012; WHO, 2012). WHO estimates that approximately 1.1 million children die, every year, due to complications associated with preterm birth (Liu , et al., 2012; WHO, 2012) Therefore, complications from preterm birth are said to be responsible for 35% of the 3.1 million neonatal deaths that occur globally every year.

In the poorest countries of the world, the percentage of preterm births is approximately 12% while higher income countries, like Canada, generally have a rate of preterm birth closer to 9%. While it is difficult to make comparisons between and among countries, it can be said that survival rate of preterm newborns varies greatly based on country of birth (WHO, 2012). A country's maternal health, healthcare services, reproductive technologies, and population demographics are all factors that influence the rate of prematurity. In low-income countries, such as those in Sub-Saharan Africa, 50% of babies born at 32 gestational weeks (GW) die due to lack of basic needs such as antibiotics and warmth. In contrast, in high-income countries, 50% of babies born much earlier (24 GW) survive preterm birth. This survival gap between countries is significant (WHO, 2012).

1.2.2 Burden, Morbidity, Mortality and Cost to Society

As stated, two major impacts of preterm births for a newborn are increased risk of morbidity and increased risk of mortality. Preterm births are the main cause of infant mortality in economically developed countries and are responsible for approximately 75% of deaths that occur in the perinatal period (about five months before and one week after birth) (McCormick, 1985; CIHI, 2009).

Higher morbidities (both short- and long-term) can result in extended hospital stays. The final several weeks of normal gestation yield 35% of brain growth and significant lung and general fetal development (Kinney, 2006; CIHI, 2009). Many preterm infants have increased rates of respiratory distress, temperature control problems, neurocognitive problems, and hospital re-admission problems when compared to full-term infants. These health issues that arise among preterm infants often extend into adulthood (WHO, 2012). Chronic illnesses that can result from complications of a preterm birth, such as cerebral palsy, can lead to a lifelong struggle and huge costs associated with care.

Neonatology is a medical subspecialty of Pediatrics that focuses on the care of newborn infants and is considered a very successful medical innovation of the 20th century. It is an innovation that was developed over many decades and requires the combination of multiple trained healthcare professionals, a variety of medical devices, and an organized administrative structure to coordinate complex interactions and technologies (Sick Kids, 2014; Lantos & Meadow, 2006). Innovation within neonatology developed rapidly. There have been instances when treatments and technologies were introduced without detailed research protocols or proper informed consent. This is particularly true with neonatal intensive care and neonatal intensive care units (NICUs). While the medical successes of neonatology are hard to dispute with hundreds of thousands of babies being saved worldwide since its beginnings in the 1940s, the long-term effects on patients and the cost burden on society are also important areas to consider for an overall health care system (Lantos & Meadow, 2006; Roback, 2006). Care of ELBW preterm infants in

developed countries almost always requires a visit to the NICU and the use of several health technologies (Oommen & Jatinder, 2010).

NICUs are units in hospitals that specialize in providing intensive care to infants with significant medical needs (Fallah, Chen, Lefebrve, Kurij, Hader, & Leeb, 2011). NICUs have multi-disciplinary teams including neonatologists, neonatal nurse practitioners, other nursing staff, clinical coordinators, clinical care managers, medical consultants (cardiologists, neurologists, nephrologists etc.), anesthesiologists, lactation consultants, pharmacists, dieticians, social workers, psychologists and occupational therapists etc. NICUs today focus primarily on the most vulnerable infants (Petrou, Eddama, & Mangham, 2011; WHO, 2012). Care for preterm infants in the NICU is the main driver in reducing morbidity and mortality in this vulnerable population. (Shah, et al., 2012).

Assessing the key drivers of costs is difficult because diagnosis is strongly correlated to pregnancy complications and maternal risk factors. Generally speaking, the higher the complications and/or risk factors, the higher the costs. Interventricular hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and patent ductus arteriosus (PDA) are complications that have also been identified as cost drivers (Korvenranta, et al., 2010).

The short and long term impact of preterm births in Canada is significant. Preterm infants have substantially higher health expenditures and hospital costs than infants who are born later than 37 gestational weeks (CIHI, 2006). For preterm infants born at <28 GWs (defined as early preterm) in 2002-2003, the average cost of hospital stays in Canada for the first ten years of life is CAD $67,467. For preterm infants born between 28-32 GWs (defined as moderate preterm), the economic burden decreases to an average of CAD $52,796 and even further for preterm infants born between 33-36 GW (defined as late preterm), at an average of CAD $10,010 (Saigal & Doyle, 2008; CIHI, 2006).

A report that examined hospital stays based on birthweight rather than weeks of gestation stated that from 2002-2003, the average cost for a newborn's hospital stay varied from

CAD $1,084 for infants with a birth weight of more than 2,500g to CAD $117,806 for preterm infants born with a birth weight of less than 750g.

In 2014, Johnston et al. studied the financial burden of prematurity in Canada over the first ten years of life. They found the national cost for all infants to be approximately CAD $587.1 million. Based on population size, national costs for early preterm infants (< 28 GW) were estimated to be CAD $123.3 million, CAD $255.6 million for moderate preterm (28-32 GW) and CAD $208.2 million for late preterm infants (33-36 GW). For all gestational ages, the largest costs were associated with the NICU (Johnston, et al., 2014).

The preterm birthrate in the United States is approximately 11.5% (Glass, Costravino, Stayer, Brett, Cladis, & Davis, 2015). In 2007, the Institute of Medicine released a report estimating the societal cost burden of preterm birth in the United States at $26.2 billion (CAD $32.8 billion as of July 26, 2017) (Institute of Medicine, 2007; OANDA, 2017). The average costs for the first year of medical expenses (both inpatient and outpatient) were reported to be $3,325 (CAD $4,158.59 as of July 26, 2017) for full-term infants and $32,325 (CAD $41,585.90 as of July 26, 2017) for preterm infants (Institute of Medicine, 2007; OANDA, 2017).

To date, most economic analyses exploring the cost of preterm care have taken a healthcare service perspective. While this perspective considers the costs directly associated with the organization, it excludes many other important factors. Taking a societal perspective, while undertaking an economic analysis of the costs associated with caring for preterm infants, would be beneficial as many individuals and organizations in society are impacted when a child is born prematurely. Long-term health issues with these children can impact society for many years (Herrod, Chang, & Steinberg, 2010).

From 2002-2003, the average cost of a NICU admission in Canada was CAD $9,700 while the average cost for a newborn of average body weight with no significant medical conditions, not admitted to the NICU, was CAD $795. Johnston, et al. reported the unit

costs for a stay in the NICU in Ontario using costing data from the Ontario Case Costing Initiative (OCCI). The unit cost for a stay in a NICU was found to be CAD $1 628.60 per day in contrast to CAD $388.00 per day for normal neonatal care (costs inflated to 2012) (Johnston, et al., 2014).

In the past, most infants entering the NICU were expected to remain within the unit until it was time for them to be discharged unless a surgical intervention was required. However, advances in treatment in the last ten years allow infants who are stable enough, to be transferred to transitional units where they can thrive and grow until they are ready to be discharged from the hospital (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). In many cases, transitional care is provided in the pediatric ward of a hospital where costs are not as high.

As of 2012, there were 30 NICUs and approximately 100 neonatologists who care for preterm babies in Canada (Janvier & Shah, 2013; Canadian Premature Babies Foundation, 2014). Maintaining physiological and thermal stability for the infant is crucial at this vulnerable stage in life (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). Inability to provide this stability puts newborns at risk for higher morbidity and even death. Transferring infants to, from, and within the NICU requires undisturbed intra-hospital transportation whenever possible. The Giraffe OmniBed with the General Electric Shuttle (GES) was introduced into hospitals to address this need.

1.3 Immature Skin, Fluid and Electrolyte Balance and Temperature Control

Throughout pregnancy, fetuses grow in a relatively stable thermal neutral environment in the mother's uterus. While in utero, infant body temperature is dependent on their mother. They maintain a temperature that is approximately 0.3°C–0.5°C higher than their mothers' (Power, Schroder, & Gilbert, 1984). In the first few minutes of life after

being born, newborns are thermally vulnerable and can suffer from significant heat loss and hypothermia due to an extreme change in ambient temperature. Their thin, immature skin provides little protection against the post-natal environment and plays an important role in thermoregulation and water balance. Immature skin can result in evaporative heat loss and water loss (Rutter, 1996).

Newborn infants have a limited ability to generate heat and to prevent heat loss to their external environment (Rutter, 1996). After birth, non-shivering thermogenesis is activated to allow for metabolic heat production within the newborn's body. Due to the developmental deficiencies of preterm infants (particularly in those born before 32 GWs), this process, along with infant activity and vaso constriction, is often inefficient causing the infants to lose more heat than they can generate through their sympathetic nervous system and brown adipose tissue. This heat loss can, in turn, result in hypothermic body temperatures that are characterized by cardiovascular collapse (Knobel, 2014; Baumgart & Touch, 2010). ELBW preterm infants have particularly thin, immature skin as their organs did not have the chance to fully develop in their mother's uterus. Due to their lack of fat reserves, large body mass to surface ratio, and poor vasomotor control, the body temperature of premature infants abruptly drops after birth (Narendran & Heath, 1999; Baumgart & Touch, 2010).

Body temperature is defined as the balance between heat loss and heat production (Knobel, Holditch-Davis, & Schwartz, 2010). The American Academy of Pediatrics guidelines defines the lower limits of a normal body temperature range for a newborn infant as 36.5°C (American Academy of Pediatrics and College of Obstetrics and Gynecologists, 2012). Hypothermia occurs when the body temperature reaches 35.5°C (Laptook & Watkinson, 2008). A temperature between 35.6°C - 36.4°C should be cause for concern among clinicians. Many studies on thermoregulation of infants, since the mid-1900s, have shown that hypothermia result in poor health outcomes with an increase in morbidities and mortality (Bassinger & Annibale, 2010). Studies have shown that hypothermic temperatures in preterm infants at admission results in a higher incidence of intraventricular hemorrhage (IVH), higher incidence of sepsis and an increase in the rate

of mortality (Laptook, Salhab, Bhaskar, & Network, 2007; Miller, Lee, & Gould, 2011; de Almeida, et al., 2014).

In order to address temperature vulnerability in newborns and how to treat it, it is important to understand how infants lose body heat. Heat can be lost in four ways: evaporation (energy consumed by a fluid as it converts into a gas), conduction (transfer of body heat to a cool object, i.e. a scale), convection (loss of heat to cooler air), and radiation (heat loss due to heat radiating from a body to another surface) (Knobel-Dail, 2014). Interventions used in the treatment of ELBW preterm infants need to address these areas of vulnerability.

Temperature vulnerability of ELBW infants can often dictate their survival rate, therefore, optimization of care practices within the delivery unit of a hospital is crucial in the first moments of a newborn's life. Immediately after birth, infants are wet and susceptible to evaporative heat loss. It is crucial to dry and wrap newborns to try and maintain the metabolic heat that they are generating (Sinclair J. C., 1976). The avoidance of lower temperatures in the delivery room promotes the stabilization of temperatures for both full-term and preterm infants (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011).

Research shows that in order to increase the survival rates for ELBW preterm infants, it is crucial that they be maintained in a neutral thermal environment (Knobel, Holditch-Davis, & Schwartz, 2010). A neutral thermal environment is an environment created either by a device or a method in order to maintain normal body temperature and, in turn, minimize caloric expenditure and oxygen consumption. Maintaining a neutral thermal environment is difficult due to an infant's transepidermal water loss (TEWL). TEWL is a quantitative measure of the movement of water from inside the body out through the epidermal layer of skin to the surrounding environment via diffusion and evaporation. It is also known as insensible water loss (IWL). Water loss can also occur naturally through the kidneys and gastro-intestinal tract (referred to as sensible water loss).

Many factors that result in TEWL contribute to morbidity and mortality in ELBW preterm infants. These factors include, but are not limited to: electrolyte imbalances and temperature instability due to increased skin vascularity, immature epithelial layers and a larger surface area (Knobel, Holditch-Davis, & Schwartz, 2010); it is, therefore, crucial to try and maintain a neutral thermal environment for ELBW preterm infants in early postnatal days to give them the best chance for survival with minimal complications. Without proper body fluid metabolism and electrolyte levels that are well balanced, ELBW preterm infants are particularly vulnerable to such morbidities as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and patent dutctus arteriosus (PDA) (Kim, Lee, Chen, & Ringer, 2010).

TEWL is partially dependent on the humidity in the newborn's environment. Optimal humidity in the ELBW preterm infant's environment improves skin integrity, thermal stability and fluid and electrolyte balances by decreasing evaporative heat and water loss from the skin (Rutter, 1996).

Best practice is to try and prevent excessive TEWL rather than replacement of excessive water loss. Various interventions and methods have been tested to stabilize TEWL and prevent severe dehydration and hyperosmolarity in ELBW preterm infants (Laptook & Watkinson, 2008). Polyethylene blankets, semi-occlusive skin barriers, intake of fluid volume, plastic hoods, sterile gastric drips, as well as humidified and non-humidified incubators are all interventions used to try and reduce evaporative heat and water losses (Sung, et al., 2013). The use of humidified incubators in particular has been reported to improve the maintenance of body temperature and reduce transepidermal fluid loss in preterm infants (Kim, Lee, Chen, & Ringer, 2010; Sung, et al., 2013). The challenge, however, is when the infant needs to be moved from an incubator to a radiant warmer for various procedures and treatment. Stabilization of temperature becomes problematic. The Giraffe OmniBed was designed to address this problem.

As a result of TEWL and immature organs, ELBW preterm infants are also particularly vulnerable to an imbalance in electrolyte levels. The newborn kidney has limited

capacity to excrete excess sodium and water. This is particularly true during the first week of life. Infants often need to receive supplemental sodium, potassium, and chloride in order to thrive. Without proper electrolyte balance, infants are vulnerable to such complications as metabolic acidosis and hypernatremia (Sung, et al., 2013).

Hypernatremia is a hyperosmolar condition that is caused by a decrease of water in the body resulting in higher levels of serum sodium. If left untreated, this imbalance can lead to circulatory issues and neuronal cell shrinkage, possibly leading to brain injury (Lien & Shapiro, 2007). Treatment requires access to the infant.

While many interventions are used for temperature management in the delivery room, over the last few decades, humidified incubators have been the most common intervention used in economically developed countries to minimize evaporative losses and thermal instability, improve fluid and electrolyte balance, and improve skin integrity for ELBW preterm infants during the most vulnerable days or weeks of their life (CIHI, 2012). Fluid and electrolyte balance can be monitored and adjusted based on the results of various outcomes. Temperature, growth (weight loss or gain), serum sodium levels, potassium levels, and glucose levels are among the most common outcomes looked at when monitoring a newborn.

1.4 Interventions and Medical Devices Used in Treating ELBW Preterm Infants

Many different health technologies have been used in the care of ELBW preterm infants in their first few weeks of life to treat thermal and electrolyte instability, some low-tech and some high-tech, some low cost and some high cost. Cot nursing, skin-to-skin care, drying and wrapping, thermal hats, plastic coverings, polyethylene blankets, semi-occlusive skin barriers, exothermic or heated mattresses, radiant warmers and humidified and non-humidified incubators are all used to help maintain stable fluid balance and stable body temperature.

Neonatal Incubators and Radiant Warmers

It is common place, even today in economically developed countries, for infants to be moved from the stable environment of a conventional neonatal incubator to a radiant warmer to allow healthcare workers access to their patients to conduct tests and procedures. Conventional neonatal incubators and radiant warmers are widely used to care for preterm infants in the NICU as they provide an environment similar to the mother's uterus (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). Neonatal incubators are biomedical devices that are used to maintain temperature, humidity and oxygen levels in a controlled environment. They are designed to limit a newborn's exposure to temperature fluctuations, noise, dust, infections, and handling (Kim, Lee, Chen, & Ringer, 2010). Incubators are enclosed on all sides, with access doors that allow professionals to observe the newborn and measure temperature, cardiac function, oxygenation, respiration, and mental activity (Baumgart & Touch, 2010). They can also provide a humid environment in order to maintain a stable fluid balance and minimize skin and respiratory evaporation (Kim, Lee, Chen, & Ringer, 2010). When placed into an incubator, newborns are equipped with a temperature sensor or probe and heat within servo-controlled incubators can adjust according to the sensor reading to maintain a constant temperature. Alternatively, the temperature can be controlled externally by a thermostat. Heated, humid air is circulated through the chamber and additional oxygen can be added as required (Oommen & Jatinder, 2010).

Regulatory bodies, such as the Food and Drug Administration (FDA) in the United States, provide manufacturers with clear guidelines on requirements for the design and performance features that neonatal incubators and transport incubators must meet for pre-market approval. The requirements for safety and effectiveness testing, including the biocompatibility of materials and device performance, are outlined in technical documents published by the IEC. Device features need to meet the need of the user and the patient and the performance features, theoretically, ensure the device is safe and effective (U.S. Department of Health and Human Services, 1998).

Characteristics of a modern day neonatal incubator include a clear plastic hood and walls that surround an insulating foam mattress with various access points for handling and caring for the patient. Hand ports within the walls allow for access with minimal interruption to temperature and warming of the neonate with larger side panels that can be opened for better access to the patient (Oommen & Jatinder, 2010).

In a conventional incubator, when healthcare professionals need full access to a newborn to perform medical procedures the newborn must be transferred to a radiant warmer. In doing so the newborn faces significant temperature changes and exposure to possible infection from its environment (Baumgart & Touch, 2010).

Radiant warmers, which are open tables with heating devices mounted above, allow easy access to a newborn, provide heat to a newborn's body and are able to constantly measure body temperature. They are designed to mitigate fluctuations in temperature and control the newborn's metabolism rate while the newborn is undergoing treatment (CIHI, 2012).

When newborns need to be transported to another location (for example another wing of a hospital), they have traditionally needed to be transferred to a transportable incubator, exposing them to fluctuations in temperature and other environmental risk factors. A challenge facing neonatal healthcare teams is transporting newborns while still providing intensive care to this population without compromising patient stability (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). The General Electric Shuttle that attaches to the Giraffe OmniBed was designed to address this transfer issue.

Other Neonatal Interventions

For the purposes of this review, other conventional interventions used to treat ELBW preterm infants are considered, as many of the interventions can be used simultaneously or in conjunction with one another. Below is a brief overview of other interventions used to maintain stable body temperatures and fluid and electrolyte balance in ELBW preterm infants:

- Cot nursing – nursing a newborn in a cot instead of an incubator so that the mother has easier access. With this intervention, additional warmth is needed for the newborn. This can be achieved through a heated room, clothing and bedding (Gray & Flenady, 2011).

- Skin-to-skin care – Also known as Kangaroo care, this practice sees the naked newborn warmed against the bare skin on the chest of the person holding them (Baumgart & Touch, 2010).

- Drying and wrapping (possibly with plastic coverings) – Immediately after birth the newborn is dried off and wrapped in soft warm blankets. In some cases, the newborn will be wrapped in plastic blankets or polyethylene (occlusive) wrap depending on what the attending staff recommends (Baumgart & Touch, 2010).

- Thermal hats – As a large amount of heat is lost through newborn's head due to his/her large surface area, a thermal hat placed on a newborn's head after birth can help to maintain a stable body temperature (Knobel-Dail, 2014).

- Thermal or exothermic mattresses - Used to provide heat to a newborn during transportation. Can also substitute for an incubator to provide heat to a newborn (McCall, Alderdice, Halliday, Johnston, & Vohra, 2014).

- Semi-occlusive skin barriers – An example of a semi-occlusive skin barrier would be polyurethane dressing that is used to create a protective barrier on immature skin to prevent moisture loss (Baumgart & Touch, 2010).

Giraffe OmniBed

Hybrid incubator-radiant warmer devices, such as the Giraffe OmniBed, were created to minimize disruption to the neonatal environment during this vulnerable time in the infant's development. This innovation aims to minimize environmental risks faced by

ELBW preterm infants when undergoing medical and nursing procedures throughout the first weeks of their lives by providing a microenvironment in which the newborn can thrive (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). This technology allows healthcare professionals to treat infants without physically moving them from one device to another, thereby mitigating risk factors (including thermal fluctuations).

Shortly after a preterm infant is born, they are transferred to the Giraffe OmniBed (General Electric Healthcare, 2015). Biomedical engineers included several features to minimize environmental risks faced by ELBW preterm infants: a Baby Susan mattress that rotates 360 degrees and slides in and out to allow for proper positioning for procedures, a layered, pressure-diffusing mattress to help preserve skin integrity, drop-down, removable doors for quick access, an elevating base that allows for height adjustment for procedures, an integrated scale to measure a newborn's growth and development, thermal and weight data trend monitors to help facilitate clinical decision-making (General Electric Healthcare, 2015). In contrast to conventional incubators, the Giraffe OmniBed has a retractable canopy hood that allows healthcare professionals to access the patient easily, as well as a servo-controlled humidifier. Because no transfer is required, the newborn's neutral thermal environment is not disturbed.

The Giraffe OmniBed is mobile when attached to the Giraffe Shuttle. This feature can help reduce the potential for physiological problems associated with an interruption in thermoregulation, and in handling or moving a newborn. When conventional technologies (separate incubator and radiant warmer) are used, a newborn must be transferred to a transport incubator in order to be moved (General Electric Healthcare, 2015).

1.4.1 Advantages and Disadvantages of Neonatal Interventions

Cot nursing, skin-to-skin care, drying and wrapping, thermal hats, semi-occlusive skin barriers, exothermic mattresses, radiant warmers, and humidified and non-humidified incubators are all used for any newborn requiring specialized medical care after birth

based on the recommendation of the attending staff. These interventions help maintain a stable fluid balance and a stable body temperature and can be used in conjunction with one another (Doctor, Foster, Stewart, Tan, Todd, & McGrory, 2017; Kim, Lee, Chen, & Ringer, 2010; Gray & Flenady, 2011).

The interventions defined as comparators in this systematic review have benefits and deficits ranging from cost to ease of use. Table 1 shows some the reported advantages and disadvantages of the interventions considered in this systematic review.

Table 1: Advantages and disadvantages of various neonatal interventions

Intervention	Advantages	Disadvantages
Cot nursing	· Reduces conductive heat loss (Knobel-Dail, 2014). · Shown to be effective in healthy preterm and low birthweight infants (Gray, Paterson, Finch, & Hayes, 2004; Knobel-Dail, 2014).	· Effectiveness unclear for ELBW preterm infants.
Skin-to-skin (Kangaroo care)	· No infrastructure or cost required. · Shown to prevent heat loss in preterm infants (Bauer, Uhrig, Pasel, Wieland, & Versmold, 1997). · Helps with parental bonding.	· No clear recommendation that it is an effective intervention for preterm infants at birth (McCall, Alderdice, Halliday, Johnston, & Vohra, 2014).
Drying and wrapping	· No infrastructure required · Inexpensive – use of warm soft blankets. · Does help prevent heat loss.	· Shown effective for term infants, however, effectiveness unclear for ELBW preterm infants (Baumgart & Touch, 2010).
Thermal hat	· Routine to place a hat on a newborn's head to prevent heat from escaping. · No infrastructure required. Minimal cost. · Polyethylene caps have been shown to help reduce occurrence of hypothermia (Trevisanuto, Doglioni, Cavallin, Parotto, Micaglio, & Zanardo, 2012)	· Have been shown to be ineffective in promoting thermal stability in newborns (Coles & Valman, 1979; McCall, Alderdice, Halliday, Johnston, & Vohra, 2014).
Thermal or exothermic mattresses	· Can be used for transport instead of an incubator. · Have been shown be as effective as incubators in warming preterm infants (McCall, Alderdice, Halliday, Johnston, & Vohra, 2014)	· Risk of hyperthermia and burning of patient if not monitored properly (McCall, Alderdice, Halliday, Johnston, & Vohra, 2014).
Semi-occlusive skin barrier	· No infrastructure required, cost effective. · Shown to reduce water loss, dermatitis and risk of sepsis (Soll & Edwards, 2000)	· Care must be used in removing semi-occlusive dressings as they can stick and cause damage to the thin, immature skin (Baumgart & Touch, 2010).
Radiant warmers	· Good for short periods of time such as to conduct surgical procedures and stabilization after birth. · Work well in combination with other interventions to maintain thermal stability (Baumgart & Touch, 2010).	· Has been shown to cause an increase in oxygen consumption and insensible water loss in newborns (Flenady & Woodgate, 2003). · Exposes infant to infection. · Hard to control for humidity.
Humidified incubator	· Studies have shown that skin maturity, thermal stability, and fluid and electrolyte balance have improved when using humidity in the care of preterm infants (Agren,	· Maturation of the skin barrier can be delayed (Knobel-Dail, 2014). · Deceases bonding experience. · Humidity can promote infection and bacterial/ fungal growth in an

	Sjors, & Sedin, 1998; Knobel-Dail, 2014) · Allows for temperature and humidity control.	incubator (Sung, et al., 2013) · Difficult access for medical professionals.
Non-humidified incubator	· Longtime standard of care, proven to prevent heat loss. · Allows for temperature control. · Good visibility of patient. · Can be servo –controlled and adjusts for temperature as needed (Oommen & Jatinder, 2010).	· May contribute to risk of infection (Knobel-Dail, 2014). · Deceases bonding experience. · Less likely to promote infection than humidified incubators however still possible due to bacterial growth. · More expensive than some of the other interventions listed.
Giraffe OmniBed	· It is both a humidified incubator and radiant warmer, requiring less space in hospital room. · Several features to minimize environmental risks faced by ELBW preterm infants including a retractable roof. · Allows for temperature and humidity control (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011).	· Requires a ceiling high enough to accommodate a retractable roof (General Electric Healthcare, 2015). · Expensive technology.

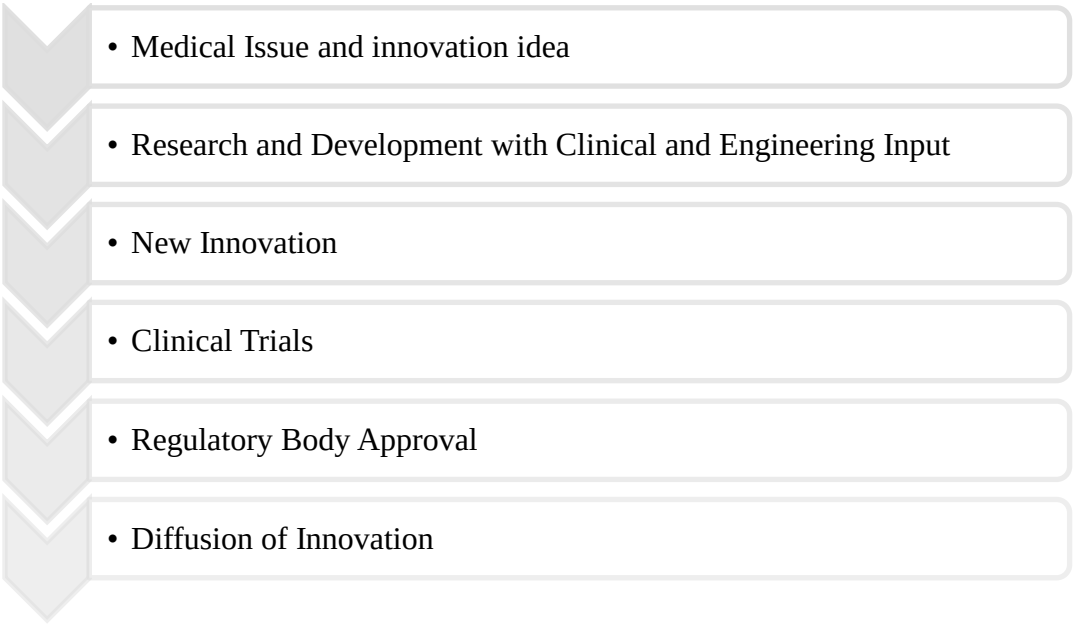

Figure 1: Standard pathway of medical device/drug innovation[1]

[1] Adapted from (Oommen & Jatinder, 2010)

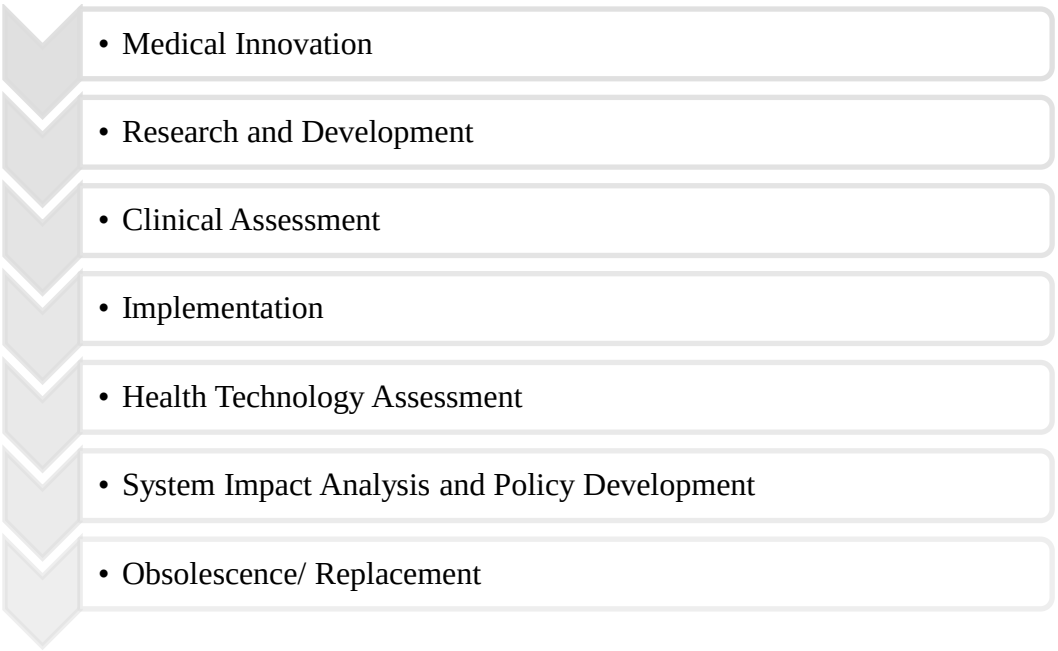

Figure 2: Standard life-cycle of a medical device with respect to policy decisions[2]

[2] Adapted from (Ferrusi, Ames, Lim, & Goeree, 2009)

2.0 Background on Systematic Literature Reviews

Systematic reviews are a large component of HTAs. Once a question is posed by a researcher or decision-maker, a systematic review of available literature should be conducted to help form a recommendation. A decision should be based on a body of evidence as opposed to the results of an individual research paper. As bodies of evidence in certain fields are constantly increasing, it is more difficult for professionals to review the full body of evidence available. Systematic reviews are done in order to identify, choose, critically appraise and synthesize the best evidence available for a particular research question. They are robust, rigorous reviews of a specific question that are used in many different disciplines to help inform decision-making and to set guidelines and policies. Systematic reviews are used as a tool to help professionals keep up with evidence that is accumulating in their particular field and as a tool that can show a lack of adequate evidence on a specific subject and demonstrate the need for further research (Boland, Cherry, & Dickson, 2014). Every systematic review on a specific research question should include every relevant study conducted on that question.

A systematic review does not rely solely on information such as expert opinion; it relies on the hierarchy of evidence ranging from less regarded case studies to highly regarded randomized clinical trials (RCTs). Figure 3 shows the general hierarchy of evidence used when summarizing the body of available research on which most researchers agree. Conducting a systematic review imposes a discipline on the summation of a body of research on a specific subject. Systematic reviews may or may not include summary statistics and a meta-analysis. A summary statistic provides an estimate of the direction and size of the treatment effect. Narrow confidence intervals (CI) demonstrate that the treatment effect is relatively precise whereas wide CIs indicate uncertainty. (Khan, Kunz, Kleijnen, & Antes, 2003; Sackett, Strauss, Richardson, Rosenberg, & Haynes, 2000).

Many organizations and collaborations have been formed over the years in an effort to provide consensus on how a proper systematic review should be carried out. One of the most well-known organizations is the Cochrane Collaboration. The Cochrane Collaboration is an international organization consisting of healthcare professionals, physicians, consumers and researchers. The organization prepares, maintains and promotes accessibility of systematic reviews in order to promote informed decision making in healthcare. Currently the organization has 37000 volunteers in over 130 countries (Cochrane, About Us, 2016).

2.1 Parameters within a Systematic Literature Review

Systematic reviews are comprised of two major components - a protocol and a final review. These components contain many steps to ensure a robust and rigorous review is performed (Boland, Cherry, & Dickson, 2014).

Overview of Steps in Systematic Review Process:

1. Identify research question, conduct a scoping search, and create a protocol
2. Literature search with defined search criteria
3. Literature screening
4. Retrieve all full text papers from literature screening
5. Rigorous literature screening with explicit inclusion/exclusion criteria
6. Literature data extraction and quality appraisal
7. Data compilation
8. Synthesis/ analysis of data (if applicable meta-analysis)
9. Write-up/ final review of what is found and the conclusions made

Many different domains can be considered when conducting a systematic review. Effectiveness and efficacy of an intervention are often considered by scientists on a continuum. Effectiveness trials follow efficacy trials. Trials that look at efficacy determine if an intervention is able to produce an expected result under ideal

circumstances. Trials that look at effectiveness determine the degree of beneficial effect of an intervention in "real world" settings (Godwin, Ruhland, & Casson, 2003; Gartlehner, Hansen, Nissman, Lohr, & Carey, 2006).

2.2 Potential Limitations

The conduct and design of the study should be robust enough for its results to be generalizable. Just because a study is published in a peer-reviewed academic journal does not mean that it is of good quality. All studies must be appraised for risk of bias by a reviewer.

A bias is a departure from the truth or systematic error in inferences or results (Cochrane Collaboration, 2011). While dealing with a large pool of published literature, it is important to try and minimize the risk of bias as much as possible.

The following reporting biases are some of the most important biases to watch for while conducting a systematic review according to the Cochrane Collaboration (Cochrane, Assessing risk of bias in included studies, 2016):

- **Selection Bias**: Choosing participants for a study that are not representative of the target population.
- **Allocation Bias**: Allocating participants into certain or pre-determined treatment groups in order to try and obtain a desired outcome.
- **Publication Bias**: Publishing or not publishing research results based on the findings. Some studies that report positive findings are more likely to be published.
- **Outcome Reporting Bias**: Choosing to include some outcomes instead of others in publications because of the effect it has on the results.
- **Funding Bias**: Certain funders could have vested interest in positive outcomes being published.

2.2.1 Addressing Potential Limitations

Specific quality appraisal tools are employed to minimize the risk of bias in systematic reviews. Appraisal tools allow a reviewer to determine if the study they want to include in their review has been designed, conducted and reported in a reliable way. Quality of evidence can be assessed in different ways. Quality of individual outcomes across studies can be considered separately and the quality of a study as a whole can be assessed.

When the quality of each individual study included in a systematic review is appraised, a higher quality systematic review results (Egger, Davey-Smith, & Altman, 2001). The quality of each study refers to the level at which any given study takes measures to minimize error and bias in its design, conduct and reporting. A quality appraisal tool answers questions: is this study robust? Is this study generalizable and trustworthy? Quality appraisal tools address questions in relation to the list of biases listed in section 2.0. The Newcastle-Ottawa Quality Assessment Scale is one such tool.

When the quality of individual outcomes across studies is appraised, methodological strength of studies, effectiveness of treatments, and consistency of results across studies are examined. GRADE, which stands for, Grading of Recommendations, Assessment, Development and Evaluation is one such tool/approach (GRADEProGDT, 2013).

2.2.1.1. The Newcastle-Ottawa Scale

The Newcastle- Ottawa Scale is a tool that was specifically designed to be an easy-to-use method to assess the quality of non-randomized studies to be included in systematic reviews (Wells, et al., 2014). It is the product of collaboration between the Universities of Ottawa (Canada) and Newcastle (Australia). The Newcastle-Ottawa Scale categorizes cohort studies into three broad domains that are subdivided and judged on eight items. The three domains include: study group selection, group comparability, and ascertainment of outcome. The tool is used by awarding stars to each of the assessment

items within each category. A maximum of four stars can be awarded to the selection category, two to the comparability category and three to the outcome category. Any given study can be awarded up to nine stars, meaning that studies of the highest quality would have nine stars. Based on the number of stars allotted, a reviewer determines the quality of the evidence and decides to either incorporate the results of the study in their review or not (Wells, et al., 2014).

2.2.1.2. The Grade Approach

The GRADE approach is a method used to assess the quality of evidence of a systematic review and strength of recommendations resulting from systematic reviews and health technology assessments (The GRADE working group, 2004). Development of the methodology began in 2000 with the collaboration of a diverse group of international guideline developers and scientific professionals. It was created to address shortcomings in previous grading systems used to help scientists create recommendations. The GRADE approach recommends that systematic reviews be used as a basis for making evidence-based health care recommendations (BMJ Clinical Evidence, 2012). The quality of evidence to be included in a systematic review is assessed by the level of confidence in the effect estimates (the body of evidence) (Cochrane Collaboration, 2011).

The quality of evidence is defined as the degree to which there is confidence that the estimate of an effect of an intervention is sufficient to support a certain decision or recommendation (GRADEProGDT, 2013). Study designs and five other factors can downgrade the confidence in the quality of evidence. Three factors can upgrade the confidence in the quality of evidence. Factors that can decrease the confidence in the estimate on an effect include risk of bias, inconsistency in results, indirectness (measured by publication bias and lack of comparability of the population, intervention and outcomes of interest to those in the included studies), and imprecision in results in the included studies. Assessment of observational studies begins with the understanding that the study is of very low quality and can only be upgraded. Factors that can upgrade the

quality of evidence include: large effect size, dose response gradient, and plausible confounding in observational studies (GRADEProGDT, 2013).

2.3 Summarizing and Synthesizing Literature

Results of the literature review should be summarized, presented and interpreted by the reviewer. The reviewer must then assess whether or not it is appropriate to combine the results found in the studies into a meta-analysis.

2.3.1. Presenting and Interpreting Results of Individual Studies

Many different types of data can be presented in various ways. For example, binary data can be presented as a summary statistic (relative risk, risk ratio or risk difference). Continuous data can also be presented as a summary statistic (mean difference of standardized mean difference). It is common to summarize results in a table format with accompanying text explaining what has been found (Boland, Cherry, & Dickson, 2014).

2.3.2. The Meta-Analysis

If individual trials are homogenous enough, a meta-analysis may be appropriate. Meta-analyses are statistical analyses of results from independent studies included in a systematic review. They aim to produce a single estimate of a treatment effect with information taken from studies similar enough to do so. Meta-analyses have the ability to enhance the precision of estimates of treatment effects, resulting in a reduced chance of false negative results (Drummond M. F., Sculpher, Torrance, O'Brien, & Stoddart, 2005).

Figure 3: Hierarchy of evidence used in research

3.0 Rationale and Research Question

3.1 Problem Statement

Health care dollars are finite. Health care funding comes mainly from taxpayers through elected governments and from donors who expect their contributions to result in excellent health care. To ensure taxpayers and donors receive value for their money, allocation of funds to purchase healthcare technology needs to be based on a body of evidence.

Decision-makers are replacing existing technologies that are used to treat ELBW preterm infants in hospitals without a body of evidence to support doing so. The adoption, diffusion and implementation of a new technology can be a costly undertaking and extremely difficult to reverse once completed. Decision-makers must be well-informed about the effectiveness, efficacy, and safety of a given technology before allocating often-scarce financial resources for their purchases.

The policies on the regulation of medical devices impact the amount and the quality of clinical evidence available on a given medical device. Without a comprehensive body of evidence, it is very difficult for HTA producers to provide decision-makers with evidence-based recommendations.

To date, no comprehensive synthesis on the body of evidence available on the Giraffe OmniBed's effectiveness, efficacy and safety versus other employed interventions has been conducted.

3.2 Study Objectives

Overall objective

To systematically locate, review and analyze original studies and summarize comparative evidence about the effectiveness, efficacy and safety of the Giraffe OmniBed as assessed by physiological indicators (body temperature, body weight, fluid and electrolyte balance); And to understand how devices like the Giraffe OmniBed are evaluated and disseminated into a health care system.

Primary objective

Compare effectiveness, efficacy and safety of Giraffe OmniBeds with other interventions currently used to treat complications of prematurity in ELBW preterm infants and to answer the research question.

Secondary objectives

After completing a systematic review of literature for the primary objective, secondary objectives were identified to help contextualize the results of the review.

1. To highlight, compare and contrast regulatory policies in Canada, the United States and the United Kingdom.
2. To highlight, compare and contrast value frameworks of national HTA agencies in Canada, the United States and the United Kingdom.

3.3 Research Question

Do Giraffe OmniBeds improve effectiveness, efficacy and safety outcomes for ELBW preterm infants?

4.0 Methods

4.1 Systematic Search of Literature

This chapter includes the methodology used to retrieve all relevant literature on the research question. Effectiveness and efficacy domains were both considered because evidence in both the real world setting and under ideal conditions is relevant to the patient population and the outcomes of interest. All domains offer insight and important information in relation to the research question. Details on the inclusion and exclusion criteria, databases searched and search strategies are all detailed throughout the chapter.

4.1.1 The PICO Scheme

Population

ELBW preterm infants (male and female)

Intervention

Giraffe OmniBeds (described previously)

Comparators

Conventional non-humidified and humidified incubators, radiant warmers, drying and wrapping, semi-occlusive skin barriers, cot nursing, thermal hats, exothermic mattresses, and skin-to skin care (previously described)

Outcomes

Primary: Episodes of hypothermia

Secondary: Growth, skin maturity, temperature difference, mortality

The PICO scheme including time period and study designs can be seen in Table 2.

4.1.1.1 Types of Participants

Participants are ELBW preterm infants and therefore must weigh less than 1,000 grams (they generally have a corresponding gestational age of 23–28 weeks)

4.1.1.2 Types of Outcome Measures

Primary outcome*:*

Episodes of hypothermia (any recorded body temperature below 35.5°C) within the first week of life.

This review focuses on outcome results during the first week of life. Hypothermia was chosen as the primary outcome because maintaining a stable body temperature is a critical for infants (Rutter, 1996). One of the primary functions of an incubator is to maintain a stable body temperature for newborns. Hypothermia in ELBW preterm infants has been associated with higher morbidity and mortality, making temperature control a critical part of neonatal care (Knobel-Dail, 2014).

Secondary outcomes:

- Growth: Weight loss expressed as a % of birthweight during the first week of life.
- Skin immaturity: fluid and electrolyte balance measured by:
    - **Total fluid intake** – expressed in ml/kg/day. Measures the fluid rate (including standard fluids, blood products, medications, etc.) during the first week of life
    - **Urine output** – expressed in ml/kg.hr. Measures the volume of urine excreted during the first week of life
    - **Serum sodium levels** – expressed in mEq/L. Measures concentration of sodium in the blood during the first week of life
    - **Potassium levels** – expressed in mEq/L. Measures concentration of potassium in blood during the first week of life

    - **Glucose levels** – expressed in mEq/L. Measures concentration of glucose in the blood during the first week of life

- Temperature difference: difference in body temperature before and after use of the intervention
- Mortality: neonatal death during the first week of life and death during initial hospitalization

Growth, skin maturity, temperature difference and mortality rate were all chosen as secondary outcomes. Maintaining a stable fluid and electrolyte balance and stable body temperature is crucial during the first few weeks of a newborn's life and their ability to thrive. These secondary outcomes were chosen because they are good indicators of fluid and electrolyte balance and temperature stability. All of the outcomes are indicators of the effectiveness, efficacy, and safety of the microenvironment that the Giraffe OmniBed provides to ELBW preterm infants.

4.1.1.3 Study Designs and Time Period

Systematic reviews, meta analyses, randomized controlled trials, quasi-randomized controlled trials, and observational studies (case control and cohort studies). These types of studies provided the best sources of information to satisfy the domains chosen for this review. Full-text, abstract publications, and unpublished data were all considered. Google Scholar and the CADTH Grey Matter Database list were searched for any additional publications and for grey literature. Only studies available in English were considered.

Relevant studies between 2001 and December 2016 were all considered and reviewed. This start date was chosen based on when the Giraffe OmniBed began to be more widely used in hospitals (Centre for Evidence-based Purchasing NHS, 2002).

4.1.2 Search Strategies for Identifying Studies

The research question was broken down into search components that could be inputted into a search engine to identify relevant literature.

Concept Building

All the PICO components were defined and taken into consideration when building a search concept Venn diagram for the review. The Venn diagram can be seen in Figure 4. The diagram shows that relevant studies include ELBW preterm infants, one of the defined outcomes of interest, and the Giraffe OmniBed.

Identification of Synonyms

In order to create a thorough search strategy, synonyms of the search component terms were identified (see Table 3). Through OvidSP and each individual search engine, synonyms were found based on defined search criteria. Searching all relevant synonyms ensures completeness of the strategy and will help yield the maximum number of relevant studies. In this review, all search components and their synonyms were searched in English.

Search Strategy

The search strategy was created in 2013 in collaboration with then Director of Hospital and Library archives at Sick Kids Hospital, Ms. Elizabeth Uleryk. A search strategy was designed for each of the search component terms and their synonyms as seen in Table 3. The Boolean operator "OR" was used to join each individual term with their respective synonyms in order to ensure all aggregates were created. The aggregates were then joined by the Boolean operator "AND" in search of all relevant studies containing all search component terms and their synonyms.

Execution of the Strategy

The complete search strategy for MEDLINE and EMBASE can be found in Appendix 1 and Appendix 2 respectively. The search strategies outlined were carried out with the

OvidSP search engine. MEDLINE and EMBASE databases were searched by 'mapping terms' either as headings or as keywords. An asterisk was applied to the end of terms that were truncated to indicate that there could be unknown characters. "Giraffe OmniBed" in various forms was searched in Google Scholar. A full search strategy can be found in Appendix 3. The search strategies included studies only published in English from January 2001 up to and including December 2016.

Study Criteria

A wide net was cast in order to find all relevant studies. Inclusion and exclusion criteria are important to define and follow. Inclusion and exclusion criteria based on the research question are listed below. Both Ms. Haig and the primary reviewer used these criteria while executing the search strategy. Studies that did not meet the inclusion criteria were excluded.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Studies published from January 2001 – December 2016
- Studies that are Giraffe OmniBed specific
- Studies that include at least one outcome of interest
- Studies that are published in the English language
- Population of the study must include ELBW neonates
- All study designs that include a relevant comparator

Exclusion Criteria:

- Studies published using a hybrid-humidified Incubator that is not Giraffe OmniBeds
- Studies that are non-comparative
- Reviews and editorials
- Studies that involve non-human subjects

4.1.3 Databases Searched

Ms. Elizabeth Uleryk provided guidance on how to correctly create a search strategy and provided recommendations on which databases should be searched for this systematic review. Preliminarily, CIHNAL, the Cochrane library, EMBASE and MEDLINE were all scanned using a search strategy created for the OvidSP user interface. CIHNAL and the Cochrane library both yielded limited results. At that time, it was decided that EMBASE and MEDLINE would be exhaustive for this review. Auto alerts were set for both EMBASE and MEDLINE through Ovid SP and were sent to the reviewer bi-weekly. In order to be exhaustive, Google Scholar was searched for additional studies as well.

To be as inclusive as possible, a manual search of keywords was done on the Canadian Agency for Drugs and Technologies in Health (CADTH) website and on the Cochrane Library website. Grey literature, literature on data that is generally not published, also needed to be considered for this review. CADTH created a tool specifically designed to exhaustively search grey literature (CADTH, 2015). CADTH's Grey Matter Database list is comprised of dozens of Canadian and International Health Technology Assessment Agencies, Regulatory Agencies, and Clinical Trial Registries. The list was used as a reference point to search for grey literature. Relevant websites that did not require a subscription on the CADTH list were all searched. A table of the websites that yielded results can be found in Appendix 3.

The International Network for Agencies for Health Technology Assessment (INAHTA) was consulted. Through this website, The National Institute for Health Research's PROSPERO database (International prospective register of systematic reviews) was accessed and searched using the keywords "Giraffe OmniBed" and "Hybrid incubator" in their general search box. The University of York's Centre for Reviews and Dissemination (CRD) search engine that accesses the Database of Abstracts of Reviews of Effects (DARE) and the National Health System Economic Evaluation Database

(NHSEED) databases was also searched using the same keywords typed into the "any field" box.

The CRD also hosts the HTA Canadian Database Repository. HTA producers from Ontario, Quebec, and Alberta partnered with the CRD to create a common repository for Canadian HTA reports within their existing international HTA Database. This site provides access to bibliographic information on ongoing and published health technology assessments commissioned or undertaken by members of INAHTA as well as other HTA organizations located around the world free of charge. These databases were searched for studies that satisfied the aforementioned inclusion criteria in this review. All of these databases were searched for the keywords "Giraffe OmniBed" or "Hybrid incubator" in the "any field" box.

References of studies were also scanned and in some cases resulted in an abstract review.

General Electric (GE) was contacted on three separate occasions to request any studies that they may have on the Giraffe OmniBed. All correspondence went unanswered. The GE website was consulted for information on the intervention.

4.1.4 Data Collection

Sourced studies from MEDLINE and EMBASE were saved and references were exported to Endnote version #6.0.1. Using Endnote to manage the literature results allowed for direct export of relevant literature from OvidSP. The software allowed for easy organization of all of the studies that were identified through MEDLINE and EMBASE and easy removal of duplicate results. Grouping results into various folders through Endnote allowed for clear organization of relevant studies for both reviewers to access them for data extraction.

Screening of Results

While conducting a broad scope on studies readily available on this subject, it was noted that there was not an abundance of information available. A large net was cast in the preliminary screening in order to ensure that all possible studies that addressed the review question were would be captured. After exportation of retrieved results to Endnote, duplicates were deleted. To ensure that all duplicates were removed, the titles were also manually searched for duplication. Any additional duplicates that were found were removed. This list of studies was sent to the secondary reviewer to conduct a fully independent screening.

Preliminary screening of results was done by applying the inclusion criteria to the titles of the retrieved references. Following inclusion or exclusion based on the title of the study, an abstract review was done of the remaining studies. If the abstract identified that the study did not fit the inclusion criteria, it was excluded at this point. To keep records organized, various folders were created in EndNote. Folders included "included studies" based on primary or secondary outcomes respectively and "excluded studies" based on primary and secondary outcomes respectively. Studies were moved into their relevant folder based on the population or intervention. After the abstract review, both reviewers reconvened in-person to discuss their results. If there was any question on whether or not a study should be included, it was kept for a full-text review.

The secondary screening required a full-text literature scan of all of the studies that were included in the review based on title and abstract screening. Full-texts were retrieved using the automated literature retrieval function in Endnote. This function worked through the University of Toronto Gerstein Library database. If the study was not able to be retrieved through this method, the Gerstein Library was searched manually. In one case, an interlibrary loan was requested through the University of Toronto. Once all of the full-text studies were retrieved, they were saved and stored and shared with the second reviewer.

Additional folders were created in Endnote to indicate which studies were included or excluded based on the secondary review of each study. Studies were moved to each of the relevant folders based on whether or not, upon further review, they met the inclusion criteria. Studies that passed this stage of screening then underwent a thorough full-text literature review. The patient drop-out rate for each study was considered. Based on the information available, no studies were excluded on these grounds.

Both reviewers followed the outlined procedure, however, some of the second reviewer's results were recorded in an excel spreadsheet instead of being stored in Endnote. Reviewers were not blinded to the trial authors' names or the institutions and were asked not to consider the authors' names and institutions in assessing the study for eligibility in an effort to reduce any possible bias. Reviewers convened and agreed upon which studies were to be included in this systematic review. A consensus on included studies was quickly reached and there was no need to include a third reviewer in the process. Results and details of the findings will be provided in the next chapter.

4.1.5 Data Extraction and Management

The primary and secondary reviewers extracted data from eligible studies into a custom-made data collection form created in Excel. After extraction was completed, both reviewers met in person to compare the results and to ensure that they were the same. Any conflicts that arose were addressed and agreed upon. The data extraction form can be seen in Appendix 5.

4.1.6 Risk of Bias Assessment in Included Studies

A key consideration in a systematic review is the degree to which the evidence found in included studies should be believed. The critical appraisal of the quality of the research is an important step to ensure that the review is based on high quality, believable evidence (Cochrane Collaboration, 2011). After data were extracted from the identified

studies, all of the studies underwent a quality appraisal using the Newcastle-Ottawa Scale to assess the internal validity of individual studies. The Newcastle-Ottawa scale is the assessment tool recommended by the Cochrane Collaboration, that measures the risk of bias for observational studies (Cochrane Collaboration, 2011). For cohort studies, the scale assesses bias through three domains: selection, comparability and outcome.

The selection domain assesses the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and if it was demonstrated that the outcome of interest was not present at the start of the study.

The comparability domain assesses the comparability of cohorts on the basis of design or analysis. It addresses confounding within the study.

The outcome domain assesses how the outcomes were obtained, if the follow-up time was long enough for the outcome to occur and if there was adequate follow-up of cohorts to ensure that loss of patients was not due to the exposure or the outcome.

The framework presents reviewers with a series of questions under each domain that are answered to determine how many stars should be given to each category and ultimately the study. Due to its thorough and customizable questions for observational studies, this tool is ideal for this systematic review. Both reviewers agreed upon the personalization of the tool where required.

The comparability section of the tool examines the comparability of cohorts on the basis of design or analysis. The first question required the reviewer to define what the studies controlled for. Part (a) considered if the study controls patient birthweight and part (b) considered if the study controls for gestational age. Outcome follow-up was assessed for the first week of life.

An example of the Newcastle- Ottawa Scale for cohort studies can be found in Appendix 6. Both reviewers referenced the manual on how to use the tool and reviewed the PowerPoint presentation that was made by the creators of the tool.

Each reviewer appraised one study first and compared results to ensure consistency in interpretation of the tool. After a consensus was reached on the use of the Newcastle-Ottawa Scale between reviewers, each reviewer quality appraised the second study independently.

4.1.7 Quality of Evidence across Studies

The GRADE approach offers a structured and transparent process for measuring the effect estimates within a study. A transparent process is essential as there is an element of judgement required when appraising the quality of evidence. The Cochrane collaboration recommends using this approach and therefore it was used to appraise the quality of evidence available across studies (GRADEProGDT, 2013; Cochrane Collaboration, 2011).

The primary reviewer discussed with a clinician outcomes that were included in this review. After consultation with a clinician and reviewing the GRADE handbook, both reviewers discussed the GRADE process and agreed on which outcomes would be included in the GRADE summary of findings table. After agreement on outcomes that were important enough to include in the summary of findings table, each reviewer separately appraised the quality of evidence and created a summary of findings table using the GRADE online tool for table creation. Where possible, the risk ratio was calculated. Risk ratio is the probability with which an outcome will occur (GRADEProGDT, 2013). Based on the assessment of the estimate of the effect of the intervention, outcomes were given an overall GRADE rating of very low, low, moderate, or high quality (GRADEProGDT, 2013). The GRADE summary of findings table can be found in Appendix 7.

4.2 Data Analysis

Data is synthesized in systematic reviews with several studies that have homogeneity between included studies to add to the generalizability of the results.

If possible, summary statistics for both binary and continuous outcomes would have been calculated. For binary outcomes (for example: episodes of hypothermia) the relative risk, odds ratio, or risk difference will be calculated along with an associated CI.

For continuous outcomes (for example: total fluid intake), which are measured on a continuous scale, the mean difference or standardized mean difference will be calculated where possible.

If possible, a meta-analysis will be carried out.

Subgroup Analysis

Literature shows that preterm infant treatment guidelines can be based on how premature newborns are and how much they weigh (degree of prematurity and birth weight). When WHO issued recommendations on care for preterm infants, many of the recommendations had an ideal weight or GA associated with them (WHO, 2015).

Therefore, the primary reviewer wanted to consider subgroups of ELBW preterm infants and preterm infants born before 29 GW to see if the Giraffe OmniBed had varying degrees of effectiveness, efficacy and safety for different subgroups of this vulnerable population.

A subgroup analysis was considered to assess treatment effects for the following subgroups:

- Gestational age: 23 – 26 weeks and 27 – 29 weeks
- Birthweight: ≤749 g; 750 g – 999 g; ≥1000 g

GA and BW were chosen as subgroup categories because they allow for a clear and concise way to separate the patient population. Examining differences in the patient population could show an optimal GA or BW at which a newborn would benefit most from being treated in the Giraffe OmniBed.

4.3 Policy Document Search

For the secondary research objectives, primary research was used to provide insight and policy context to the review. Canada, the United States (U.S.) and the United Kingdom (U.K.) were chosen for comparison. These three jurisdictions were chosen because they are all high-income, English-speaking countries with well-developed health care systems. All three jurisdictions have vibrant medical device markets, extensive medical device regulatory policies, and established national HTA programs that vary enough for comparative purposes.

National regulation policies of the three jurisdictions were sourced through an investigation of each country's regulatory agency's website. Websites were located separately through Google with a keyword search of "regulation of medical devices" with each respective jurisdiction. Websites included:

- Health Canada, TPD website
- Government of Canada – Justice Laws website
- U.S. Department of Health and Human Services
- U.S. Food and Drug Administration website
- Government of U.K., the National Archives website
- Medicines & Healthcare products Regulatory Agency website
- EUR-lex, access to European Union Law website

Internet website searches were also performed to find relevant supplemental policy documents such as journal articles and policy reports. The aforementioned Google search also yielded policy reports and other websites on the regulation of medical devices

that provided additional insight into the regulatory approval processes of each country. Supplementary publications were located on the IMRDF and WHO websites. Relevant literature was also found in the references of published studies and reports.

Value frameworks used by national HTA agencies in Canada, the U.S. and the U.K. were also compared. Websites of national HTA agencies were located separately through Google with a keyword search of "health technology assessment of medical devices" with each respective country. Websites used included:

- Canadian Agency for Drug and Technologies in Health (CADTH) website
- The Agency for Healthcare Research and Quality (AHRQ) website
- The Kaiser Permanente Centre for Health Research website
- The National Institute for Health and Care Excellence (NICE) website
- The National Institute for Health Research (NIHR) website

Internet website searches were also performed to find relevant supplemental policy documents such as journal articles and policy reports. The aforementioned Google search also yielded policy reports and other websites with valuable insight on the HTA of medical devices and the frameworks used to assess them.

Journal articles, policy papers, and reports were also located by searching publications on the websites of international organizations that have HTA initiatives. Websites searched included:

- Health Technology Assessment International (HTAi) website
- International Network of Agencies for Health Technology Assessment (INAHTA) website
- The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) website
- EUnetHTA website
- World Health Organization (WHO) website

- Advanced Medical Technology Association (AdvaMed)

Relevant literature was also found in the body and the references of studies and reports found on the websites listed above.

Table 2: The PICO Scheme

	Search Component	Definition
P	Participants	ELBW Preterm infants
I	Intervention	Giraffe Omnibed
C	Comparator	Conventional nonhumidified and humidified incubators, radiant warmers, plastic hoods, drying and wrapping, semi-occlusive skin barriers, sterile water gastric drips, exothermic mattresses, cot nursing, thermal hats, and fluid intake via intravenous
O	Outcomes	Primary: Episodes of hypothermia Secondary: Growth, Skin maturity, Temperature difference, Mortality
T	Time Period	January 2001 – December 2016
S	Study Design	Randomized controlled trials, quasi-randomized controlled trials, observational studies, systematic reviews, and meta analyses

Table 3: Search component term synonyms

Search Component Terms	Synonyms
Incubator and Infant	incubator/ or ((infan* or neonat* or newborn* or premature* or preemie* or ELBW) adj3 (warmer* or radiant or incubator*)).ti,ab. Or low birth weight/ or extremely low birth weight/ or small for date infant/ or very low birth weight/ or prematurity/ or newborn intensive care/ or newborn intensive care nursing/ or nicu*
Giraffe OmniBed	"Giraffe* bed*" or Giraffebed* or "Giraffe-bed*" or "Giraffe* omnibed*" or "Giraffe* omni-bed*" or "hybrid humidified incubator*" or "hybrid microenvironment* device*
Clinical Trial	ct.fs. or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or crossover procedure/ or double blind
Body Temperature (Primary Outcome, episodes of hypothermia. Secondary outcome, temperature difference)	body temperature/ or rectum temperature/ or body temperature disorder/ or accidental hypothermia/ or chill/ or cold clammy skin/ or fever/ or hyperpyrexia/ or hyperthermia/ or hypothermia/ or shivering/ or thermoregulation/ or temperature acclimatization/ or humidity/ or moisture/ or microclimate/ or air conditioning/ or exp humidifier/ or indoor air pollution/ or room ventilation/ or workroom air/ or skin temperature/ or temperature/
Skin Maturity (Secondary Outcome)	(skin adj2 (matur* or immatur*)).ti,ab. or "functions of the skin and its appendages"/ or skin conductance/ or exp skin function/ or skin penetration/ or skin permeability/ or skin sensitivity/ or skin sensitization/ or skin/ or exp dermis/ or exp epidermis/
Metabolic Balance (Secondary Outcome)	metabolic balance/ or acid base balance/ or exp electrolyte balance/ or fluid balance/ or kallikrein kinin system/ or (insensible adj2 (fluid* or water) adj2 loss*).ti,ab. or (Water adj2 Electrolyte adj2 Imbalance
Body Weight (Secondary Outcome)	body weight/ or birth weight/ or liveweight gain/ or weight change/ or weight control/ or weight fluctuation/ or weight gain/ or weight reduction/

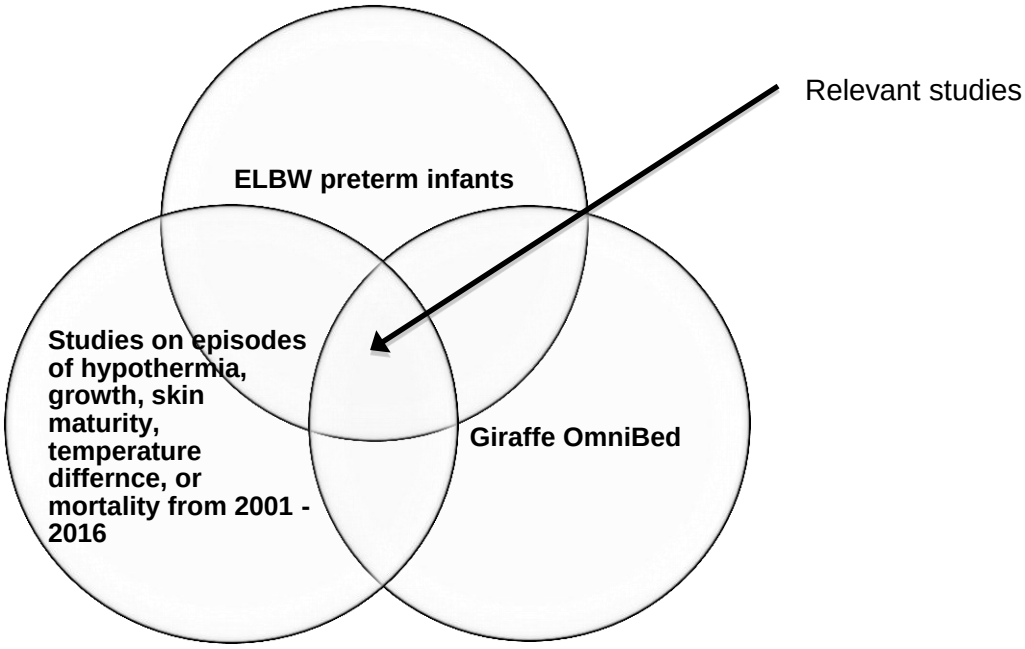

Figure 4: Concept Venn diagram of PICO

5.0 Results

5.1 Search Results

Articles included in this review were sourced through MEDLINE, EMBASE, Google Scholar, the CADTH grey literature tool, CRD databases, and references of studies found using the aforementioned resources. Articles from the start of 2001 through 2016 were considered. The Giraffe OmniBed received regulatory approval in the United States and Canada in 2000 and started to be more widely used in a hospital setting in 2001 (U.S. Food and Drug Administration, 2000; Government of Canada, 2000).

A Prisma diagram of the inclusion process for this review can be seen in Figure 5. In total, 2,274 studies were sourced and considered for inclusion in this review. The diagram shows that 2,258 citations were found using MEDLINE and EMBASE through OvidSP. Google Scholar produced 12 citations that were believed to possibly have relevant data and 4 citations were found in the references of other studies. The CADTH Grey Literature Search had 37 hits, and the CRD databases yielded no results. Through Endnote and visual scanning, 361 duplicate citations were deleted leaving 1,913 for title and abstract review. After the title and abstract review, 98 studies remained to be reviewed in greater detail. A rapid full-text scan resulted in the exclusion of 81 studies leaving 17 for a full-text in-depth review. As the remaining studies needed to undergo a thorough full-text review, data extraction was done during this review in the interest of consolidating efforts. A rigorous review process was followed while going through the full-text review. The 17 studies included studies that either mentioned the Giraffe OmniBed specifically or a hybrid humidified incubator. Upon full-text review, any study that did not specifically mention the Giraffe OmniBed was excluded immediately. Any study that may have mentioned the Giraffe OmniBed but did not report on the predefined outcomes was also excluded immediately. During the full-text review, 15 studies were excluded leaving 2 publications for inclusion. Both publications included were observational retrospective cohort studies. One was a full-text article and one was an oral

presentation abstract. As information on the topic is limited, the abstract significantly adds to the body of evidence available. Both reviewers agreed on the included studies. A table detailing the reason for inclusion/ exclusion for the 98 studies that underwent a rapid full-text review can be found in Appendix 4.

5.1.1 Description of Studies

Two studies were included in this review. These include:

- **Loersch 2007** Loersch, F., Schindler, M., Dahlmann, S., Berlet, I., Lynman, L., & Schaible, T. (2007). From traditional incubator to developmentally-oriented care by using a hybrid (OmniBed). *Journal of Paediatrics and Child Health*, 43, A26.
- **Kim 2010** Kim, S. M., Lee, E. Y., Chen, J., & Ringer, S. A. (2010). Improved care and growth outcomes by using hybrid humidified incubators in very preterm infants. *Pediatrics*, 125, e137–e145.

Information detailing the characteristics of these studies can be found in Table 4 and Table 5.

Loersch 2007 is a published abstract of an oral presentation of an observational retrospective cohort study. The study aimed to compare the impact on thermal stability and stress on admission for infants treated in the Giraffe OmniBed versus more traditional caregiving methods. The study examined 50 participants that were stratified into two groups: 31 infants with a BW of < 1500g (range from 540g-1490g) and 19 sick children. Rectal body temperature was measured for all participants. The mean body temperature was compared with a historical control group of 50 infants transported from the delivery room to the NICU in conventional incubators (Loersch, Schindler, Dahlmann, Berlet, Lynman, & Schaible, 2007).

Kim 2010 aimed to identify and compare changes in body temperature, fluid and electrolyte management, growth and other short-term outcomes in ELBW preterm infants nursed in humidified hybrid incubators (HI group) with patients cared for in non-

humidified conventional incubators (CI group). The hybrid humidified incubator used in this study was a Giraffe OmniBed.

The study originally included 227 infants but 45 were excluded. Reasons for exclusion included: incomplete data for one patient, six received care in both interventions, twenty-three died before post-natal day (PND) 7, five were transferred to another hospital before PND 7, three had severe congenital heart disease, four had multiple congenital abnormalities, and three had severe hydrops. In total, 87 were included in the CI (conventional incubator) group and 95 included in the HI (hybrid incubator) group. Primary outcomes observed included: body temperature, fluid and electrolyte balance, and growth. Secondary outcomes included: mortality, and morbidity. Morbidities included: occurrence of PDA, BPD, NEC, intraventricular hemorrhage and sepsis (Kim, Lee, Chen, & Ringer, 2010). Participants had a mean ±SE gestational age of 26.9 ± 0.2 for both the HI group and the CI group. The mean ±SE birthweight for the HI group was 768.0g ± 14.8g and 789.2g ± 15.7g for the CI group (Kim, Lee, Chen, & Ringer, 2010).

Heterogeneity between the two studies was high; otherwise, a meta-analysis would have been carried out if possible. Unfortunately, there was not enough data available to produce a meta-analysis. Ideally there would have been several studies with many estimate effects that could have been pooled and statistically analyzed.

5.2 Risk of Bias Assessment in Individual Studies

5.2.1 Results of Newcastle –Ottawa Scale

A thorough risk of bias assessment of both studies was conducted. Results of can be seen in Table 6.

Loersch 2007 was assessed to have a high risk of bias. As Loersch 2007 is an abstract, there is a lack of information available with no information given about the comparator

group. This study was never published as a full journal article (Loersch, Schindler, Dahlmann, Berlet, Lynman, & Schaible, 2007).

While the abstract published by Loersch et al. did not report any conflicts of interest or funding, the fourth writer on the study worked for GE Healthcare in the United States. A study published by Loersch et al. in 2011 on the transportation of newborns in a hospital setting disclosed that Mannheim University Klinikum was supported by GE Healthcare-Maternal Infant Care for the study. All of this was taken into consideration as a possible conflict of interest.

Kim 2010 was deemed to be of moderate risk of bias as the patient population was somewhat representative of the premature newborn community and the non-exposed cohort was drawn from the same community. The study controlled for patient birthweight between cohorts and all subjects were followed-up over a long enough period of time for the outcomes of interest to be measured. This was a well done observational study that had a rigorous study design (Kim, Lee, Chen, & Ringer, 2010). The fact that neonate who died during the first week of life introduced bias into the study. Not only does this impact the mortality rate but excluding early deaths can also have an impact on reporting of other outcomes.

5.3 Reporting of Findings

Results for the outcomes of interest can be found in Table 7. None of the studies reported on potassium levels, glucose levels or mortality for the first week of life.

5.3.1 Episodes of Hypothermia

Neither of the studies reported detailed information on episodes of hypothermia. Kim 2010 did, however, report that there were body temperatures recorded at less than 35.5°C and that there was no significant difference in the number of episodes of hypothermia

between the HI group and the CI group. Loersch 2007 reported that no patient treated in the Giraffe OmniBed had a rectal temperature of less than 36.1°C.

5.3.2 Temperature Difference

Loersch 2007 reported the average rectal temperature at admission for all infants to be 36.71°C (median range: 36.2°C - 37.3°C). For infants who were < 1500g the average body temperature was 36.65°C. Avg. Temp was 0.49°C higher than the historical control group of 50 infants ($p<0.0001$). After operations in the Giraffe OmniBed, no newborn had a rectal temperature of less than 36.1°C.

Kim 2010 set out with the goal of maintaining a stable axillary and abdominal skin body temperature range. They reported body temperature values at first admission and at day 0 for both groups, and then at PND 1-3. The mean ±SE for body temperature for the CI Group was 35.8 ±1.0°C and 35.7 ± 0.9°C for the HI Group at first admission. The authors reported no significant difference between the two groups on any day that their temperature was taken.

Kim et al. also examined patient subgroups defined by body weight (BW) regardless of intervention. Infants with a BW of ≥750g had a mean ±SE body temperature of 36.0 ±0.8°C at first admission and 36.6°C ±0.3°C at day 0. Infants with a BW of ≤749 g had a mean ±SE body temperature of 35.3 ±1.1°C at first admission and 36.2°C ±0.5°C at day 0. Those patients with a BW of ≥750g had a higher body temperature at first admission versus day 0 than those with a BW of ≤749 g. The authors found that BW at a given gestational age was a strong predictive factor for body temperature by using mixed design multiple regression ($P< .0001$ for the HI group and $P= .0467$ for the CI group).

5.3.3 Growth

The weight of a newborn can be influenced by such factors as co-morbidities, caloric intake, and the use of postnatal steroids (Kim, Lee, Chen, & Ringer, 2010). The growth of a patient can be measured by the percentage of their weight gain or loss after birth. Loersch 2007 did not report on weight gain or loss.

Kim 2010 reported on the percentage of weight loss during the first week of life. Infants were weighed every day before feeding. During the first week of life, the CI group, that was weighed outside their incubator, showed a higher maximum body weight loss of 10.9 ±0.7% versus the HI group, that was weighed within the Giraffe OmniBed, and had a maximum body weight loss of 8.3 ±0.6% (P=0.011). This difference was seen in both subgroups with the CI group having a significantly higher weight loss than the HI group. Broken down between intervention and BW subgroups, patients with a BW of ≥750g showed an 11.9% weight loss in the CI group versus 8.7% in the HI group. For patients with a BW of ≤749g the CI group had a weight loss of 9.2% versus 6.9% in the HI group.

5.3.4 Skin Maturity

Skin maturity can be measured by fluid and electrolyte balance of the skin (Rutter, 1996). Information published on fluid and electrolyte balance, including total fluid intake, urine output, and sodium levels was extracted for the purposes of this review. There was no information provided on potassium levels and glucose levels.

5.3.4.1 Total Fluid Intake

Fluid intake is controlled through feeding tube or intravenous. The mean ±SE total fluid intake was reported as ml/kg/day. Kim 2010 reported on the mean ±SE total fluid intake of their patient population for the first week of life. The HI group was found to have a

mean ±SE of 161.6 ±3.5 ml/kg/day and the CI group was found to have a mean ±SE of 180.6 ±4.9 (P<0.001).

5.3.4.2 Urine Output

Kim 2010 reported on the mean ±SE urine output for the first week of life. They did not detail how urine output was measured. Amount of excreted urine was recorded hourly for the first week of life. The HI group had a significantly lower hourly urine output reported at 3.7 ±0.2 ml/kg/h versus the CI group at 4.2 ±0.2 ml/kg/h (P<0.0001).

5.3.4.3 Na^+ Levels

Kim 2010 reported on the serum sodium level of their patient population and incidence of hypernatremia. They defined hypernatremia as Na^+ > 150 mEq/L. In the first week of life the HI group had a lower maximum serum sodium concentration of 145.3 ±0.5 mEq/L versus the CI group that had a maximum serum sodium concentration of 147.2 ±0.7 mEq/L (P=0.026). The HI group had a lower incidence of hypernatremia at 10.5% than the CI group at 20.7% (P =0.026).

5.3.4.4 Mortality

Kim et al. started with a patient population of 227 ELBW infants. Of these, 235 patients were excluded from the study due to death before PND 7. The authors of this study were contacted several times for more information on this exclusion with no success. It is unknown if the 23 patients were treated in a Giraffe OmniBed or a conventional incubator when they died during their first week of life.

5.4 Results of the Grade Approach

The GRADE approach Summary of Findings table along with explanations can be seen in Appendix 7. Based on the recommendation of clinicians, five outcomes were determined to be important enough to be assessed with the GRADE approach and be included in the Summary of Findings table. Serum sodium level was not included for appraisal. Two reviewers independently assessed the quality of the evidence for outcomes across included studies.

Episodes of hypothermia was defined as a critically important outcome for ELBW preterm infants. Evidence on the effect of the Giraffe OmniBed on episodes of hypothermia was assessed to be of very low quality.

Body temperature, weight loss, total fluid intake and urine output were all defined as important outcomes and the quality of evidence reported for all of them was deemed to be of very low quality. Risk of bias was high across outcomes.

5.5 Results of Grey Literature Search

The CADTH Grey Matter search for grey literature yielded information about recalls of the Giraffe OmniBed. In Canada, the device was recalled on three separate occasions, April 25, 2005 - June 27, 2005, December 28, 2012- February 18, 2013 and November 13, 2016- December 13, 2016 for unintentional movement of the elevating base following a main power disruption, for fluctuations in the oxygen and radiant heater set point following a power failure, and for a safety issue with the power cords respectively. These recalls, although important, were not discussed in the studies that were included in this review.

A 2002 report by the Medical Device Agency at the National Health Service (NHS) in the U.K. provided a detailed overview of the Giraffe OmniBed when it first came to

market including a description of the device, survey results from users and the device's and manufacturer's information. The "user assessment" portion of the review showed that overall professionals using the device viewed it favourably. The users (neonatal nurses and doctors) believed that the rotating mattress, the humidity function, and its ability to function as both an incubator and a radiant warmer were advantages. They believed the price of the device was high at £ 29 000 (CAD $67 189 as of January 1, 2002), for the most basic model, but they valued the streamlining of treatment process (Centre for Evidence-based Purchasing NHS, 2002; OANDA, 2017).

5.6 Results of Policy Document Search

Regulation Policy Scan

The initial secondary objective was to highlight, compare and contrast regulatory policies of medical devices in Canada, the United States and the United Kingdom. The policy scan revealed that Canada, the U.S. and the U.K. all have extensive medical device regulations based on patient safety and device functioning. While the policies share many of the same principles, differences exist between and among jurisdictions. Table 8 shows a summary of regulation of medical devices and HTA landscapes in Canada, the U.S. and the U.K.. All three countries have national regulatory agencies that enforce legislation on the regulation of medical devices in their respective countries. All three countries classify their devices based on the level of risk that is associated with the intended use of the device.

While the classification of devices in all countries is based on level of risk and intended use of the medical devices, classification and regulatory requirements for each Class varies between countries. Table 9 details the Classes of devices, their associated level of risk, and the regulatory requirements each Class of device must meet to gain access to the market in that country. Canada and the U.K. both have four classes of devices, while the U.S. has three. In all three countries the classes are defined differently and all have

different regulatory requirements in order to gain market clearance. Class I devices require little more than registration with their national regulatory authority. In Canada, Class II and III devices both require a medical license. They both require efficacy, safety, and performance information, with Class III devices requiring more detailed documentation including information on any clinical trials. Class II devices in the U.K. are subdivided into Class IIa and Class IIb depending on level of risk associated with the device. All devices undergo a conformity assessment by a Notified Body in order to receive a CE mark. Class IIb require additional performance and reliability testing related to their safety and intended use. Regulation of Class II devices in the United States differs completely from the others with a 510(k) review process that relies on substantial equivalence to a predicate device that already received regulatory approval. Class IV devices in Canada, Class III devices in the U.K. and in the U.S., all have the most rigorous requirements to gain market access.

A clear comparison of regulatory processes across all three countries can be seen in Table 10. All countries have their own national regulatory authority that is responsible for carrying out regulatory activities in their respective countries. Each country has an explicit definition of a medical device, a detailed device classification system, essential safety and performance requirements, conformity assessment bodies, manufacturer establishment registration requirements, adverse event reporting, assessment of non-compliance, and recall systems in place. Details of these findings will be further compared in the discussion.

National Health Technology Assessment Initiatives Scan

The other secondary objective was to highlight, compare and contrast value frameworks of national HTA agencies in Canada, the United States and the United Kingdom. All three countries have national HTA initiatives with national HTA agencies that help provide recommendations on coverage and reimbursement decisions. Details on the HTA initiatives of all three countries can be found in Table 11. Each of the national

HTA agencies has serval outputs in addition to HTA reports. They all provide recommendations on coverage and reimbursement for their respective national health plans.

As the AHRQ in the United States works with various agencies on technology assessment, one of the EPC's that creates reports for them was chosen. Representatives from the EPC at the Kaiser Permanente Centre for Health Research participated in the HTAi 2017 Policy Forum, and therefore information on their framework was available. Kaiser Permanente Research Affiliates (KPRA) have two offices in the United States, one in Oregon and one in Hawaii. They not only work with the AHRQ, but also work closely with Kaiser Permanente, the largest non-profit health plan insurance provider in the United States. Table 12 shows value framework criteria used by CADTH, NICE and KPRA in Canada, the U.K. and the U.S. respectively. This table was adapted from a report created from the 2017 HTAi policy forum (Oortwijn W. , 2017). Criteria varied among countries. While CADTH and NICE had similar criteria with respect to economic evaluations, KPRA only considers an economic analysis after they have received a positive review of outcome evidence and they are preparing a strategy for deploying the health technology.

CADTH is the only agency that takes budget impact, severity of disease, and availability of treatment alternatives into account while producing their assessment; however, it does not consider social values or preferences like NICE does. All three of the agencies use their value frameworks for various health technologies and interventions. Using the framework to assess the value of allocating resources towards a specific medical device may need to include different or additional criteria, like user experience.

Medical device specific value frameworks are continuously being developed and improved by organizations like the ISPOR Medical devices and diagnostics special interest group and the Advanced Medical Technology Association in the United States (AdvaMed). Multiple stakeholders are considered in the development of their device-

specific value frameworks, including, but not limited to, the medical device industry, payers, policy makers, and health care providers (Oortwijn W. , 2017; AdvaMed, 2017).

The Medical Device Innovation Consortium (MDIC) at the FDA presented a working framework in 2015 that incorporated patient preferences into the regulatory assessment of a medical device. The Framework developed by MDIC in cooperation with the FDA and Deloitte is intended to improve the understanding of the FDA and sponsors on how patient preferences with respect to benefit and risk might be incorporated into the regulatory review process for innovative medical devices (Medical Device Innovation Consortium, 2015).

Table 4: Study Characteristics

First Author, Publication Year, County	Study Name	Study Design	Aim	Patient Characteristics	Intervention	Comparator	Outcomes
Loersch, F., 2007, Germany & United States	From traditional incubator to developmentally-oriented care by using a hybrid (OmniBed)	Retrospective Observational study	To compare the impact of using a Giraffe OmniBed for thermal stability and stress on admission to the infants with other traditional methods	50 participants. 31 with a BW of < 1500 g, 19 sick children	Giraffe OmniBed	Conventional Incubator	Body Temperature (rectal)
Kim, S. M., 2010, United States	Improved care and growth outcomes by using hybrid humidified incubators	Retrospective Observational study	To identify and compare changes in BT, fluid and electrolyte management, growth, and short-term outcomes in ELBW infants nursed in humidified hybrid incubators (HI group) with patients cared for in non-humidified conventional incubators (CI group)	227 infants admitted during study period but 45 were excluded for various reasons leaving 182 ELBW infants. 95 infants in the HI group and 87 infants in the CI group	Hybrid Incubator (Giraffe OmniBed)	Conventional Incubator	Primary Outcomes: Body Temperature, fluid and electrolyte balance, growth velocity. Secondary Outcomes: Mortality, occurrence of PDA, BPD, NEC, IVH, and sepsis. Secondary outcomes were presented as Morbidities.

Table 5: Patient Characteristics

First Author	Study Title	Mean ±SE Gestational Age (weeks)	Mean ±SE Birthweight (g)
Loersch 2007	From traditional incubator to developmentally-oriented care by using a hybrid (OmniBed)	NR	NR
Kim 2010	Improved care and growth outcomes by using hybrid humidified incubators	HI group: 26.9 ± 0.2 CI group: 26.9 ± 0.2	HI group: 768.0 ± 14.8 CI group: 789.2 ± 15.7

Table 6: Results of Newcastle Ottawa Quality Appraisal

	Selection	Comparability	Outcome	Total
Loersch 2007	❋		❋	2
Kim 2010	❋❋❋	❋	❋❋	6

Table 7: Outcome Results

First Author	Episodes of hypothermia	Body Temperature	Mean Weight Loss (as % of birthweight) ±SE	Mean Total Fluid Intake (ml/kg/day) ±SE	Urine Output (ml/kg/hr) ±SE	Serum Sodium Concentration (mEq/L) ±SE	Mortality	Glucose Concentration (mEq/L) ±SE	Potassium Concentration (mEq/L) ±SE
Loersch 2007	NR	Avg. rectal temp. at admission: 36.71°C (median range: 36.2 - 37.3°C). VLBW (< 1500g): avg. body temp. was 36.65°C. Avg. Temp was 0.49°C higher than historical control group of 50 babies (p<0.0001). After operations in the Giraffe OmniBed, no baby had a rectal temp. of less than 36.1°C.	NR	NR	NR	NR	NR	NR	NR
Kim 2010	No significant difference between CI group and HI group.	First admission: **CI Group**: 35.8 ±1.0°C **HI Group**: 35.7 ± 0.9°C *For both groups*: BW of ≥750g: First admission: 36.0 ±0.8°C Day 0: 36.6°C ±0.3°C (closer to normal body temperature than BW of ≤749, (P<0.0001)) BW of ≤749 g: First admission: 35.3 ±1.1°C Day 0: 36.2°C ±0.5°C	First week of life: **HI group**: 8.3 ±0.6% BW of ≥750g: 8.7% BW of ≤749g: 6.9% **CI group**: 10.9 ±0.7% (P=0.011) BW of ≥750g: 11.9% BW of ≤749g: 9.2%	First week of life: HI group: 161.6 ±3.5 CI group: 180.6 ±4.9 (P<0.001)	First week of life: HI group: 3.7± 0.2 CI group: 4.2 ±0.2 (P<0.0001)	First week of life: HI group: 145.3 ±0.5 CI group: 147.2 ±0.7 (P=0.026)	NR for first week of life	NR	NR

Table 8: Summary of Regulations of Medical Devices and National HTA Initiatives in Canada, the U.S. and the U.K.

Country	National Regulatory Agency	National Regulation Policy for Medical Devices	Year	Medical Device Classification System	National HTA Initiatives	Brief description of National HTA Processes
Canada	The Health Products and Food Branch at Health Canada where The Therapeutic Products Directorate has a designated Medical Devices Bureau (TPD)	The TPD applies the Food and Drug Regulations and the Medical Devices Regulations (SOR/98-282) under the authority of the Food and Drugs Act (R.S.C., 1985, c. F-27) (Minister of Justice, 2017; Minister of Justice, 2017).	1985 1998	Classification is based on level of risk associated with the intended use of the device (Minister of Justice, 2017).	Yes	Much of Canada's HTA efforts are overseen by CADTH. Provincial bodies and hospital-based units also provide funding recommendations to decision-makers. The Pan Canadian HTA Collaborative was formed in 2011 facilitate information sharing between HTA agencies (CADTH, 2017).
The United States of America	The Food and Drug Administration's Center for Devices and Radiological Health (CDRH).	The FD&C Act, Chapter V, Medical Device Amendments in 1976 (updates include the Medical Device User Fee and Modernization Act of 2002) (U.S. Food & Drug Administration, 2017)	1976, 2002	Classification is based on the risks associated with the device and by evaluating the amount of regulation required to provide reasonable certainty of the device's safety and effectiveness (U.S. Food & Drug Administration, 2017).	Limited.	National HTA processes in the U.S. have changed a lot over the years. Currently the AHRQ provides technology assessments to the CMS to inform national coverage decisions for Medicare (Agency for Healthcare Research and Quality, 2018).
The United Kingdom	Medicines & Healthcare products Regulatory Agency (MHRA)	The Medical Device Regulations No. 618 (as amended in 2002) and the General Product Safety Regulations 2005 (SI 2005 No 1803) under the Consumer Protection Act of 1987. These legislations use three EU device directives for guidance on market access. On May 5, 2017 regulations in the EU were amended again and take full effect in 2020 (MHRA, 2017).	1987 2002 2017	Classification is risk based and considers: length of time device is intended to be used continuously, invasiveness of the device, if the device is implanted or not, and whether or not the devices contains a medicinal substance (MHRA, 2017).	Yes.	NICE provides evidence-based guidance to the NHS. Recommendations on drugs are mandated to be adopted and funded within three months. Recommendations on a medical device are provided to different stakeholders as decisions on reimbursement are made at the local level. (National Institue for Health and Care Excellence, 2017)

Table 9: Device Classification and Premarket Requirements by Country

Level of Risk	Low	Low to medium	Medium to high	High
	Class I	**Class II**	**Class III**	**Class IV**
Canada[3]	Does not require a MDL but does require an MDEL.	Require an MDL documents that show efficacy and safety in addition to an ISO 14385:2003 quality systems certificate.	Require an MDL that requires many documents in addition to an ISO 14385:2003 quality systems certificate. A detailed premarket review that includes a description of the device, the design philosophy, a summary of all preclinical and clinical studies, test reports, and copies of device packaging and labelling.	Require an MDL. This requires a full risk assessment, manufacturing specifications, and process validation reports on top of the documentation required for a Class III device.
	Class I	**Class II**		**Class III**
The United States of America[4]	Required to be registered with the FDA but generally exempt from premarket notification (510k) and FDA clearance before market access.	Usually required to go through the 510k review process. If manufacturers can prove substantial equivalence to a predicate device then a clinical trial is usually not required to prove clinical safety and effectiveness for 510k approval. Special labelling may be required.	NA	Require the most rigorous approval process. Safety and effectiveness evidence from clinical trials is usually required for the stringent PMA application.
	Class I	**Class IIa**	**Class IIb**	**Class III**
The United Kingdom[5]	Must be declared to a Notified Body who may ask for quality standard details before approving a CE mark.	Devices require a declaration of conformity to requirements listed in the MDD and the MDR. Manufacturers decide the appropriate assessment listed in the Annex of the MDD and apply for a CE mark from a Notified Body.	Require more detailed documentation on top of that required for a Class IIa device to receive a CE mark from a Notified Body. These assessments include performance and reliability testing related to their safety and intended use.	Require the most documentation to receive a CE mark from a Notified Body. Assessments required may include a design dossier examination and an audit of the full quality assurance system among other requirements outlined in the MDD and MDR.

[3] (Health Canada, 1984) (Minister of Justice, 2017) (Minister of Justice, 2017)

[4] (U.S. Food & Drug Administration, 2017) (U.S. Food & Drug Administration, 2004)

[5] (European Commission, 1993) (European Council, 1993) (MHRA, 2017)

Table 10: Comparison of Regulatory Processes[6]

	Canada	The United States of America	The United Kingdom
National Regulatory Authority	✓	✓	✓
Medical device defined	✓	✓	✓
Classification based on level of risk	✓	✓	✓
Essential safety and performance requirements	✓	✓	✓
Use of predicate devices for market access		✓	
Premarket Approval by National Authority	✓	✓	
CE mark for market approval			✓
Conformity assessment bodies	✓	✓	✓
Manufacturer establishment registration	✓	✓	✓
Post-market surveillance by National Authority	✓	✓	✓
Mandatory adverse event reporting to National Authority	✓	✓	✓
Assessment of non-compliance	✓	✓	✓
Recalls by National Authority	✓	✓	✓

6 (World Health Organization, 2016a; World Health Organization, 2016b; World Health Organization, 2016c)

Table 11: Overview of National HTA Agencies by Country

Country	National HTA Agency	Website	National Agency Outputs[7]	Additional Information
Canada	CADTH	https://cadth.ca/	HTA reports Optimal use reports Therapeutic reviews Formulary reviews Rapid response reports Environmental scanning reports Technology overviews Methodological reports	CADTH uses a value framework to help decision-makers make informed decisions on the allocation of health care resources.
The United States of America	AHRQ	https://www.ahrq.gov/	HTA reports EPC evidence-based reports Fact sheets Full research reports Quality & disparities reports AHRQ research studies	Some Evidence-based Practice Centres (EPC) that create reports for the AHRQ use value frameworks when creating reports that focus on the allocation of health care resources. i.e. Kaiser Permanente Research Affiliates (KPRA)
The United Kingdom (England)	NICE	https://www.nice.org.uk/	HTA reports Economic evaluations Quality standards Clinical guidelines Public health guidelines Social care guidelines Implementation tools	NICE uses a value framework to help inform decision-makers allocate funds for valuable health technologies.

[7] Information on outputs was sourced from their respective websites

Table 12: Value Framework Criteria used by CADTH, NICE and KPRA[8]

Criteria	Canada (CADTH)	The U.K. (NICE)	The U.S. (EPC - KPRA)
Types of technologies assessed with value framework	Drugs; Devices; Procedures, diagnostics, tests and surgeries; Public health interventions; Systems (services) delivery	Drugs; Devices; Procedures, diagnostics, tests and surgeries; Public health interventions; Systems (services) delivery	Drugs; Devices; Procedures, diagnostics, tests and surgeries; Public health interventions; Systems (services) delivery
Information requirements	Clinical benefit; economic information required to establish value for money in health. Other evidence on equity, public health, and budget impacts	Clinical benefit; health economic information required to establish value for money. Additional evidence on societal preferences, equity impacts, and budget impacts	KP seeks published clinical trials, KP research, compiled health outcome data, registries, and KP expert opinion. The clinical expert opinion from KP health care professionals is used to guide the problem formulation for the analysis and to understand current clinical practice and operational considerations, including available alternatives
Therapeutic value assessment uses the QALYs	✓	✓	
Economic value assessment:			An economic evaluation is not required as part of the evidence review of a given technology.
Cost Utility Analysis	✓	✓	
Cost-Effectiveness Analysis	✓	In some cases	
Cost-minimization Analysis (CMA)	✓	TAP uses a cost-comparison value framework.	
Patient subgroup analysis required or considered	✓	✓	✓
Aspects of value assessed:			
Size of therapeutic effect	✓	✓	
Quality of clinical evidence	✓	✓	
Burden/prevalence of disease	✓	✓	

8 Adapted from Oortwijn, W. (2017). *Background Paper, 2017 Policy Forum. From theory to action: Developments in value frameworks to inform the allocation of health care resources.* Retrieved February 2018, 5, from HTAi:https://www.htai.org/index.php?eID=tx_nawsecuredl&u=0&g=0&t=1520580352&hash=2e338af2b1457e751b537f3384b53b4011ae5172&file=fileadmin/HTAi_Files/Policy_Forum/HTAi_Policy_Forum_2017_Background_Paper.pdf

	Canada (CADTH) cont'd	The U.K. (NICE) cont'd	The U.S. (EPC - KPRA) cont'd
Relevant clinical endpoints	✓	✓	
Clinical uncertainty	✓	✓	Qualitatively assessed
Cost-effectiveness (and degree of uncertainty in economic analyses)	✓	✓	Consideration would be after a positive review of evidence, when deployment strategy is being determined.
Quality of clinical and economic modelling evidence	✓		Considered if available. Economic modelling would be considered after the evidence review if KPRA is a determining deployment strategy.
Budget impact	✓		Consideration would be after a positive review of evidence, when deployment strategy is being determined.
Severity of disease	✓		
Availability of treatment alternatives	✓		
Public health impact	✓		
Legal/ethical/equity considerations	✓		✓
Patient affordability			Considered after a positive outcome from an evidence review. KP would be mindful during the evidence review of a technology that has the potential to provide a safe, high quality outcome that is more affordable than alternatives. This is a qualitative criterion.
Social values/preference		✓	Qualitatively assessed

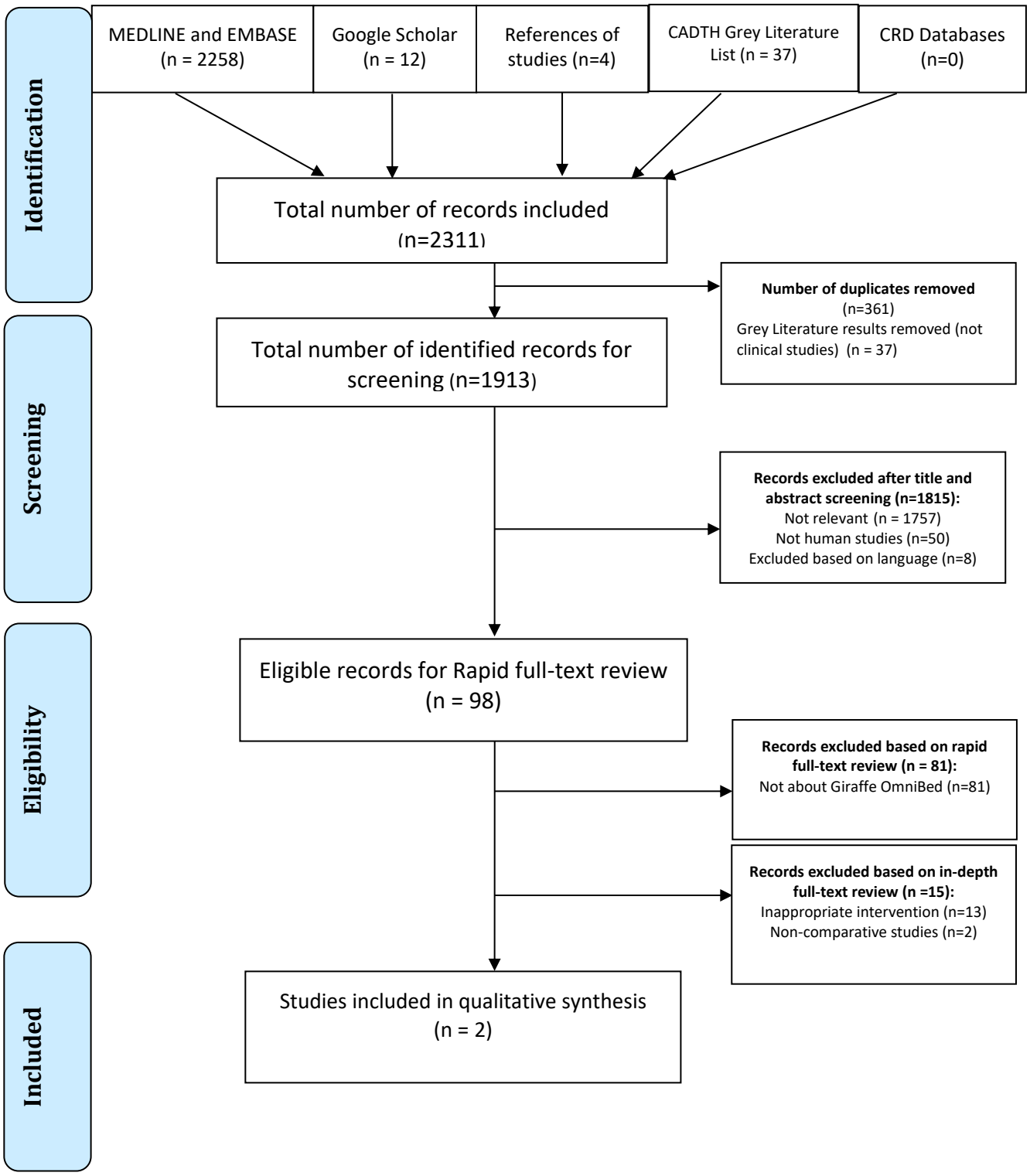

Figure 5: Prisma flow diagram of studies included in review

6.0 Discussion

Treatment and prevention of preterm births is an important area for continued research, innovation, and intervention. Vulnerable preterm babies cannot speak for themselves. While there are high financial costs of caring for preterm infants, both in the short and long-term, it is the ethical responsibility of healthcare teams to provide the preterm population with the best care possible. It is imperative, therefore, that the use of any health technology used in the treatment of preterm infants be evidence-based in terms of effectiveness safety.

Those responsible for the regulation and allocation of healthcare resources must do so responsibly and methodically. Using health technology assessment as a tool to inform decision-makers on the effectiveness, safety, cost-effectiveness and socio-economic impact of a medical device should be an important step in the decision-making process. However, a thorough and rigorous HTA requires strong clinical evidence on the medical device and the outcomes of interest.

This review focused on the Giraffe OmniBed and the most vulnerable population of preterm infants. It set out to discover if the Giraffe OmniBed improves effectiveness, efficacy and safety outcomes of ELBW preterm infants in comparison to more traditional intervention strategies. A very limited amount of evidence was found on the outcomes of interest.

Two reviewers applied the inclusion criteria to the results of the searches. Two studies were sourced for inclusion in this review. The lack of evidence was somewhat surprising as the Giraffe OmniBed is widely used in high-income countries around the world. Nonetheless, by employing an exhaustive search strategy and supplementing the results of the electronic search engines with searches for grey literature and searches of references, it is believed, with confidence, that all relevant research was found and

included in this systematic review. Data were extracted for all studies and the Newcastle-Ottawa Scale determined that individual studies were of high and moderate risk of bias. The GRADE approach was used to assess outcome evidence across studies and determined evidence to be of very low quality. The evidence included in this review suggests that ELBW preterm infants treated in the Giraffe OmniBed may improve thermal stability, improved growth outcomes and better skin maturity over patients treated in a conventional incubator, however, the conclusion cannot be drawn with certainty due to the very low quality of evidence.

The evidence or lack thereof, highlights a larger issue with respect to the lack of clinical evidence available for all medical devices. While drugs must undergo a number of different phases of clinical trials during their regulation process, medical devices do not require the same rigor in order to gain pre-market approval (Conference Board of Canada, 2017). Governments all over the world are struggling to find a balance between providing patients the opportunity to access modern medical technologies while prioritizing patient safety and economically sustaining their healthcare system (Tarricone, Torbica, & Drummond, 2017). The level of evidence required by regulatory authorities for some medical devices has resulted in a lack of evidence available for researchers to source and use in systematic reviews, meta-analyses, economic evaluations, or HTAs. HTAs are important tools for decision-makers to use when deciding which medical devices to diffuse into their healthcare system. HTA of medical devices is a changing landscape that is constantly adapting to address the lack of RCTs available and the need to provide evidence-based recommendations on medical devices in a timely manner. When HTA agencies struggle to find data to satisfy the value framework of an HTA, it makes it extremely difficult for them to provide decision-makers with transparent, evidence-based recommendations (Fronsdal, et al., 2012; Fuchs, Olberg, Panteli, & Busse, 2016).

The following sections will discuss the methodological strengths and limitations of the review, key findings of the literature, a comparison of hybrid incubator-radiant warmers available on the market, regulation policy and national HTA initiatives for medical

devices in Canada, the United States (U.S.), and the United Kingdom (U.K.) and implication of this research along with ethical considerations.

6.1 Methodological Strengths and Limitations

This systematic review used a strong methodology to allow for generalizable findings. The methodological quality and risk of bias of the included studies was evaluated to determine the confidence with which the conclusions are generalizable to the entire population of ELBW preterm neonates. The methodology of this review was strengthened by the application of GRADE approach. The GRADE approach allowed for the critical evaluation of study biases and factors that compromise the quality of the evidence across studies.

The search strategy was extensive and explicitly documented in the methods section of this review for transparency and reproducibility. When the inclusion criteria were applied to the search results, however, only two applicable studies were found. It was surprising how little comparative literature there was on outcomes for ELBW preterm infants cared for in the Giraffe OmniBed.

Even though a large body of evidence was not found, it is believed that all relevant literature available was captured in this review through the use of electronic search engines and manual searches of references. It can be said, with confidence, that the conclusions made in this systematic review are based on all the current relevant comparative research available on the topic.

Two reviewers followed a clearly outlined systematic approach to ensure that this review was methodologically sound. Reviewers followed the protocol and the rigorous review process outlined in the methods section. Having two reviewers reduced the risk of selection bias being introduced into the review.

Limitations exist within this review. This includes restricting the review to studies published in the English language. Limiting the search to studies only available in English could have potentially reduced the amount of applicable literature found. While efforts were made to include all the relevant studies available, some may have been missed because of the selected databases. Concentrating only on electronic database searches could introduce bias; however, an extensive search was done within these electronic databases in order to reduce that bias as much as possible. Although unlikely, it is for these reasons that the literature included in this review may not fully represent the current literature available.

The primary researcher's judgement was used when selecting appropriate comparators for this review. Many interventions were chosen as comparators to be as inclusive as possible. The interventions chosen as comparators in the review were both recommended by a clinician are sourced from peer-reviewed literature to account for possible bias. While it is believed that all of the interventions were appropriate comparators, future research may want to compare more interventions to the Giraffe OmniBed or different ones.

A meta-analysis to synthesize the data that were extracted from included reviews was not possible to perform. While a meta-analysis would have been the ideal way to analyze the data, it was not possible given the limited about of data found. Statistical analysis across studies was not possible. A qualitative approach was taken to synthesize the limited, low quality data, which can always introduce bias. A subgroup analysis was planned; however, the lack of high quality evidence available and the small number of studies in the present review precluded a robust analysis.

Specific limitations within individual studies were also taken into consideration. Kim 2010 declared that its study is limited by retrospective examination. To account for this limitation, Kim et al. chose a study period that they believed was long enough to capture all differences in care. Loersch 2007 is a conference abstract and therefore lacks many details of the methods and results. Loersch 2007 was assessed to be of high risk of bias

and Kim 2010 was appraised to be of lower risk. The overall number of studies and number of participants included in the review fail to provide a basis for robust analyses and conclusions.

6.2 Key Findings from Literature

This systematic review set out to answer the question: Do Giraffe OmniBeds improve effectiveness, efficacy and safety outcomes for ELBW preterm infants?

This review identified two comparative studies that evaluated the effectiveness, efficacy and/or safety of the Giraffe OmniBed. While the evidence suggests that the Giraffe OmniBed may indeed improve some of the outcomes of interest, this cannot be said with great confidence as all the evidence available is of low quality.

6.2.1 Episodes of Hypothermia and Temperature Difference

Episodes of hypothermia were chosen as the primary outcome for this review because of how crucial thermal stability is for ELBW preterm infants in their first week of life. Hypothermia has been linked to higher morbidity and mortality and therefore is a crucial outcome to consider when determining care of ELBW preterm infants. A device that provides an ELBW preterm infant with the most stable environment possible must be given full consideration by decision-makers.

Evidence in this review demonstrates that ELBW preterm infants are able to maintain a stable body temperature when being treated in the Giraffe OmniBed. The very low quality evidence even suggests that the Giraffe OmniBed could improve the thermal stability of a patient who needs to be moved throughout the hospital and require several procedures.

In 2012, Kaczmarek et al .published a non-comparative, observational study that examined the correlation between relative humidity exposure over time and fluid and electrolyte balance. The study published by Kaczmarek et al. supports the finding that the Giraffe OmniBed provides ELBW preterm infants with an environment that results in thermal stability in the patient (Kaczmarek, Tarawneh, Martins, & Sant'Anna, 2012).

It cannot be said with certainty, based on the very low quality of evidence available that the Giraffe OmniBed can impact the number of episodes of hypothermia or thermal stability in ELBW preterm infants throughout their first week of life. While there is not enough information available to make a well-informed conclusion, evidence suggests the Giraffe OmniBed provides ELBW preterm infants with a stable thermal environment.

6.2.2 Growth

Growth was reported as percentage of weight loss with respect to birthweight. Very low quality evidence showed that the use of the Giraffe OmniBed versus a conventional incubator is associated with an increase in growth, particularly in ELBW preterm infants weighing less than 749g.

Based on the limited, very low quality evidence provided by only one study, the Giraffe OmniBed appears to improve growth outcomes in ELBW preterm infants. A large degree of caution should be used when making statements about the effectiveness of a device when using the results of a single study. Weight loss and fluid and electrolyte balance in a newborn can be influenced by a baseline disease as well. BPD, NEC, and PDA have all been shown to be associated with weight loss in preterm infants (Sung, et al., 2013). Future studies done on effectiveness outcomes for infants treated in the Giraffe OmniBed should take these baseline diseases into consideration. Weight loss also speaks to skin maturity and fluid and electrolyte balance.

6.2.3 Skin maturity: fluid and electrolyte balance (total fluid intake, urine output, serum sodium levels, potassium levels, glucose levels)

A variety of factors are taken into consideration when discussing the skin maturity of an ELBW preterm infant. While reviewers found comparative evidence on total fluid intake, urine output and serum sodium levels, there was no comparative research available on potassium or glucose levels. Evidence found on skin maturity was considered to be of very low quality.

Serum sodium levels indicate if a newborn has hypernatremia. Hypernatremia is a hyperosmolar condition that is caused by a decrease of water in the body resulting in higher levels of serum sodium that can result in circulation issues that can intron result in devastating neurological deficits (Lien & Shapiro, 2007). Indication of hypernatremia can be used to guide fluid and electrolyte management.

Very low quality evidence showed that the Giraffe OmniBed is effective in decreasing insensible water loss (IWL) in ELBW preterm infants. Favourable fluid intake and serum sodium levels were seen for ELBW preterm infants cared for in the Giraffe OmniBed. This was particularly true for ELBW preterm infants under 749g. Kaczmarek et al. supported these findings as they reported the fluid intake of their patient population to be in the same range that Kim et al. did (Kaczmarek, Tarawneh, Martins, & Sant'Anna, 2012).

IWL is associated with humidity levels. Humidification was an important factor to consider when discussing skin maturity. A study conducted by Sung et. al. used the Giraffe OmniBed to treat ELBW preterm infants with high humidification. They investigated fluid and electrolyte balance in infants that were less than 24 gestational weeks during the first postnatal week under high (95%) humidification (Sung, et al., 2013). Sung et al. found that infants born at 22GW and 23GW weeks had higher IWL and need for fluids than those born at 24GW and 26GW and cared for in Giraffe OmniBeds that are set to at high humidification. The studies by Kim et al., Kaczmarek et.

al. and Sung et al. all made it clear that settings in the Giraffe OmniBed need to be individualized to each patient as their outcomes dictate (Sung, et al., 2013; Kim, Lee, Chen, & Ringer, 2010; Kaczmarek, Tarawneh, Martins, & Sant'Anna, 2012). Features on a Giraffe OmniBed allow for extensive monitoring and quick changes to a treatment pathway.

Evidence suggests that under certain settings the Giraffe OmniBed improves skin maturity outcomes for ELBW preterm infants; however, this is based on the low-quality evidence of one study. Further studies that consider organ maturation should be done to confirm this. With the current body of evidence, it is not possible to say with confidence that skin maturity outcomes are indeed improved for ELBW preterm infants treated in the Giraffe OmniBed.

6.2.4 Evidence from Additional Studies and Reports

A study by Loersch et al. in 2010 reviewed risk factors that infants face when being transferred within a hospital. They stated that neonatal thermal stability while being transported from the labour and delivery room to the NICU (a very critical phase in neonatal life) was significantly improved while using the Giraffe OmniBed versus the conventional method of a transport incubator (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). The time taken to transport the newborn was shown to be significantly less with the Giraffe OmniBed than with the conventional method, also improving the newborn's quality of life by causing less stress and allowing the baby to rest peacefully. Although it is believed that the Giraffe OmniBed decreases the amount of time a newborn needs to spend in an incubator, no published evidence has proved that assertion (Loersch, Schindler, Starr, Moore, & Lynam Bayne, 2011). The study further showed that the use of the device decreased bed transfers from 4 microenvironments (delivery room warmer, delivery scale, transport incubator, and NICU incubator) to 1 microenvironment (Giraffe OmniBed). Staff efficiencies improved as time of birth to NICU admission was reduced by eight minutes with the Giraffe OmniBed compared to

the conventional transport incubator. The authors concluded that the primary goal of a health care team should be choosing a device for short movement within a hospital with the features of a Giraffe OmniBed (one that, in their opinion, minimizes physiologic, thermal and developmental stress while maintaining constant care to the newborn).

In 2013, a Toronto hospital paid $71 300 for a Giraffe OmniBed with an in-bed scale but without an oxygen monitor and all of the available accessories. This price also did not include the Giraffe Shuttle that is needed for intra-hospital transportation of a newborn. It is a significant purchase for any institution.

In 2015, Rosin et al. presented the abstract of a prospective comparative study that concluded the General Electric Shuttle is a safe method to transport infants being treated in the Giraffe OmniBed. Evidence such as this is particularly valuable to decision-makers at a local-level who are responsible for procurement and must consider how introducing a new device into their institution can impact how the institution functions.

6.2.5 Comparable Hybrid Incubator-Radiant Warmer Devices

The medical device industry is a lucrative and competitive one (Trade and Development Canada, 2014). While the Giraffe OmniBed was one of the first hybrid incubator-radiant warmers on the market, several others have followed. Table 13 shows other hybrid incubators-radiant warmers devices that compete with the Giraffe OmniBed. The Giraffe OmniBed and the Versalet 7700 (Hill Rom, Air Sheilds) were the first two hybrid devices on the market. The Dual incu *i* (Atom Medical Corporation) and the Babyleo TN500 (Draegerwerk AG & Co. KGaA) entered the market much later than the Giraffe OmniBed and the Versalet 7700. When manufacturers of the Dual incu *i* and the Babyleo TN500 applied to the regulatory body in the U.S. (FDA), they were able to cite the Giraffe OmniBed as a predicate device. In the United States, Class II medical devices are able to gain faster pre-market approval if they are deemed to be substantially equivalent to the predicate device described in their application. An extensive comparison of

components between the Babyleo TN500 and the Giraffe OmniBed was submitted to the FDA for a 510(k) clearance by Draeger showing device equivalence. The manufacturer received clearance, based on this equivalence, without submitting any evidence from animal studies or clinical studies (U. S. Food and Drug Administration, 2017).

Some early studies that manufacturers conducted to acquire regulatory approval for hybrid incubator-radiant warmers were done with animals. In 2001, in a study sponsored by Hill-Rom Air Shields, Greenspan et al. looked at the thermal stability of nine lambs in the Versalet 7700 versus a conventional warming bed and incubator manufactured by the same company. The study showed that the hybrid device and the conventional method were both effective at maintaining temperature stability. The difference was seen in the number of adverse events in the group transitioned between devices. The Versalet 7700 required fewer temperature probes and transition of the infant between devices resulted in dislodged support lines. The authors stressed the importance of patient management and stated that the separate incubator and warming device were closer in the trial than they would have been in an active NICU (Greenspan, Cullen, Touch, Wolfson, & Shaffer, 2001). This study further supports the finding that the Giraffe Omni Bed provides a stable thermal environment for preterm infants.

Many similar devices can be found on the market at any given time because devices do not receive the same secure patent protection as drugs do. The unique chemical make-up of a drug and its application is well-defined and clearly protected by a patent for twenty years in Canada, and similar timelines in other high-income countries (Ferrusi, Ames, Lim, & Goeree, 2009). Minor modifications can be made to the composition of existing medical devices to create similarly functioning devices that do not breach the patent protection of the original device. This lack of patent protection does not afford medical devices the same market exclusivity as drugs receive for a defined period of time (Ferrusi, Ames, Lim, & Goeree, 2009).

Once a medical device is granted access to a market, payers must decide whether or not to purchase the technology and which manufacturer to purchase it from. Many high-

income countries have some sort of mechanism to incorporate HTA in the process of decision-making around policy-making, procurement and reimbursement of health technologies like a hybrid incubator radiant warmer (Conference Board of Canada, 2017). While some governments are moving towards regulatory policy where their regulatory agencies work together with HTA agencies, coverage bodies, and industry to try and support innovation and fast access to high quality care, others lack such coordination (Fronsdal, et al., 2012). The policy-oriented nature of HTA lends itself to a close integration into the functioning and governance of health systems (World Health Organization, 2011).

6.2.6 Summary of Key Findings and Future Research

The Giraffe OmniBed is an expensive intervention used in the treatment of preterm infants, yet there is very little published evidence on its effectiveness, efficacy, and safety.

In theory, the combination of humidified incubator and radiant warmer in one device sounds like an ideal intervention for treating and caring for infants. The idea that, by minimizing environmental risks in decreasing the number of times a newborn needs to be moved and exposed to various environmental factors, makes sense. While the literature reviewed suggests that the Giraffe OmniBed could be better than conventional incubators in maintaining thermal stability, improving skin maturity and growth outcomes for ELBW preterm infants, these findings are based on very low quality evidence for outcomes that were reported on; Therefore, it is not possible to conclusively say that outcomes are indeed improved as sufficient high quality evidence is not available.

This systematic review of the effectiveness, efficacy, and safety outcomes for the Giraffe OmniBed highlights the need for further research to be done on hybrid incubator-radiant warmers. This review provides a benchmark for healthcare professionals to continue research.

From specific humidity settings based on outcomes to nutritional needs, ELBW preterm infants need to be individually assessed and treated. In some situations, a combination of interventions is needed and healthcare professionals need to be able to optimize the use of the interventions available to them (Sung, et al., 2013). Future research should aim to expand from the current body of evidence available and address the conceptual and methodological limitations of studies. Future studies should be done on all the outcomes considered in this review, particularly the ones defined as critical: episodes of hypothermia and mortality. Researchers may also want to consider oxygen consumption and cardiac functions in future researchers as they are also good indicators of the infants state of health.

Ideally, future research would include RCTs that have a clear comparator and a clearly defined population. Factors affecting the population that should be taken into consideration include: immaturity of organs (the skin in particular) and baseline diseases. Ideally researchers would report on all applicable comparators that they believe provide similar benefits to ELBW preterm infants that the Giraffe OmniBed offers. While RCTs would be ideal, there are ethical considerations around the randomization of ELBW preterm infants into a given treatment group. Blinding would also be very difficult. The role of observational real-world studies as sources of clinical evidence for medical devices will be discussed in detail in a later section.

The lack of comparative evidence found on the Giraffe OmniBed in this review suggests that uptake of the hybrid device happened internationally without an evidence-based recommendation from an HTA agency. The Giraffe OmniBed is not unique in the lack of evidence available on its safety, efficacy, and effectiveness. This systematic review also highlights the lack of evidence available for medical devices as a whole. While governments say that patient safety is a priority, their regulations for medical devices do not always require robust clinical evidence on safety before issuing regulatory approval.

Most devices also lack the evidence required for a robust economic evaluation and HTA to be carried out. Some researchers are addressing this issue by examining the regulation of medical devices, how they interact with HTA in a real-world setting, examining the best time to carry out an HTA, and considering the procurement process of a medical device as a continuous spectrum (Henshall, Bayne, Frondsal, & Klemp, 2011).

To better understand how devices like the Giraffe OmniBed become available worldwide without substantial clinical evidence, a policy scan was done comparing the regulatory and National HTA processes for medical devices in Canada, the United States and the United Kingdom (with a focus on England).

6.3 Regulation of Medical Devices in Canada, the United States, and the United Kingdom

The policy scan showed that the regulation of medical devices is complex and varies among countries. Some countries include HTA in their regulatory and procurement processes but most do not. Internationally, efforts are underway to harmonize criteria within the medical device regulatory commercialization process for regulators, HTA agencies and decision-makers (Conference Board of Canada, 2017). While organizations like WHO and IMDRF are working to harmonize medical device regulations worldwide, differences exist (World Health Organization, 2017; IMDRF, 2014). Canada, the United States, and the United Kingdom all have detailed regulations for medical devices unique to their respective governments. Regulatory processes for medical devices in Canada, the U.S. and the U.K. are discussed in detail in the following sections.

Medical Device Regulation in Canada

The regulation of medical devices and the safety and efficacy data required for them to reach the market is significantly different than for pharmaceuticals in Canada (Conference Board of Canada, 2017).

As stated, Health Canada's TPD evaluates and monitors the effectiveness, quality, and safety of medical devices nationwide. They strive to ensure good outcomes through a combination of pre-market review, post-approval surveillance and quality systems during the manufacturing process (Government of Canada, 2007). Regulation of medical devices in Canada is governed through the Food and Drugs Act of 1985 (Minister of Justice, 2017). The TPD enforces the Food and Drug Regulations and the Medical Devices Regulations (SOR/98-282) (CMDR) under the authority of the Food and Drugs Act (R.S.C., 1985, c. F-27) (World Health Organization, 2014).

Detailed Premarket Regulations

Pre-market regulation includes a product assessment, device classification, quality systems, and medical device licensing (World Health Organization, 2018).

While Class I devices do not require a medical device license (MDL), they do require a medical device establishment license (MDEL), as do all devices entering the Canadian market. This license is awarded to devices that are in compliance with safety, effectiveness and labelling requirements as outlined in the CMDR. Through these licenses, Health Canada is able to exert control over importers and distributors of medical devices (Government of Canada, 2007).

Manufacturers of medical devices requiring a medical device license in Canada (Class II, III, IV) must submit an International Organization for Standardization (ISO) 13485:2003 quality systems certificate with their license application to Health Canada prior to advertisement, import or sale of the product. This certificate is obtained from a registrar who is recognized by the Standards Council of Canada. The registrar conducts a third-party compliance audit, at the expense of the manufacturers, to ensure that they have met the requirements of the national regulations. Requirements for medical device license applications depend on the class of the device a manufacturer is applying for (Government of Canada, 2017; Ruth, 2010; Minister of Justice, 2017).

A Class III medical device license application requires many documents in addition to a ISO 14385:2003 quality systems certificate. A detailed pre-market review that includes a description of the device, the design philosophy, a summary of all preclinical and clinical studies, test reports, and copies of device packaging and labelling must be submitted. A Class II device application requires less detail while a Class IV device application requires a lot more documentation including, but not limited to, a risk assessment, manufacturing specifications, and process validation reports (Minister of Justice, 2017). All licenses come with a cost and must be renewed annually. If a manufacturer wants to make changes to a licensed device, an application for an amended licence must be completed before changes are put into effect (Health Products and Food Branch Inspectorate, 2015). All applications are reviewed by the Medical Devices Bureau which can take up to six months to process an application due to backlog in the system (Ruth, 2010).

At every stage in the process, the submission must meet Health Canada's requirements for acceptability, safety and effectiveness. If the application submitted to the TPD is deemed unacceptable at any step in the process, more information must be submitted by the manufacturer for clarification. Health Canada issues an approval or refusal letter based on all of the information submitted (Health Canada, 1984).

Detailed Post-market Regulations

Post-market regulatory activities in Canada include: licensing inspections, mandatory problem reporting, handling of complaints, maintaining distribution records, implant registration, and recall management (Minister of Justice, 2017).

Distribution Records

Manufacturers must maintain meticulous distribution records of all medical devices. Records must be detailed enough to allow for the rapid removal of a device from the market should it be necessary (Minister of Justice, 2017).

Complaint Handling

Manufacturers must maintain records of all problems filed about performance characteristics and safety of the device. They also must have a strategy in place to deal with complaints and issue recalls when necessary (Minister of Justice, 2017).

Mandatory Problem Reporting

Manufacturers must report any problems that occur with any of their devices sold in Canada, even if the problem occurred outside of Canada. Problems include any incident that demonstrates deterioration in the effectiveness of a device or the failure of a device. Any event that led to serious health problems for a patient or the death of a patient must also be reported (Minister of Justice, 2017).

Recalls

Before a manufacturer can issue a recall, they must submit a detailed document to the Minister of Health outlining details of the device, details of the reason for a recall, the number of units affected, a strategy to prevent reoccurrence of the problem, and a communications strategy to deal with the recall (Minister of Justice, 2017).

Medical Device Regulation in the United States

The Medical Device Amendments to the Food, Drug and Cosmetic Act (FD&C) in 1976 gave the FDA control over the regulation of medical devices in the United States. Since then, updates to the FD&C include the Medical Device User Fee and Modernization Act of 2002 (Sorenson & Drummond, 2014). The Centre for Devices and Radiological Health (CDRH) at the FDA is responsible for assuring that devices have a certain level of safety and effectiveness before granting manufacturers market access (Lamph, 2012). Before a device can be marketed in the USA, a manufacturer must follow five steps to receive market clearance from the FDA.

First, a manufacturer must classify its device. Class I poses the lowest risk while Class III poses the highest risk (U.S. Department of Health and Human Services, 2018).

Second, a manufacturer must determine what type of premarket application they are required to submit to the CDRH. The most common submissions include: a 510(k) Premarket Notification, a Premarket Approval (PMA) application, a De Novo application (Evaluation of Automatic Class III Designation) or a Humanitarian Device Exemption (HDE) application. A 510(k) is the most common application processed. It is used for some Class I devices and almost all Class II devices. The 510(k) process requires a manufacturer is show that its device is "substantially equivalent" to a previously cleared device (US FDA, 2017). If proven, additional clinical evidence on safety and effectiveness is usually not required, however, performance standards and post-market surveillance may be addressed. De Novo applications are for Class I or II devices that were not able to prove substantial equivalence to a predicate device. While exceptions do exist, most Class III devices require the most rigorous application, a PMA application. A PMA application requires clinical evidence of the safety and effectiveness of the device. An HDE is used for devices that are used to treat rare diseases (less than 4000 patients) (Kramer, Xu, & Kesselheim, 2012; U.S. Department of Health and Human Services, 2018).

Steps three, four, and five have the manufacturer prepare all of the documents required for their submission, send the submission while interacting with staff from the FDA to address issues with the application, and complete an establishment registration and device listing respectively (U.S. Department of Health and Human Services, 2018).

The Giraffe Omni Bed is classified as a Class II device in the United States. It received 510(k) clearance in 2000 by showing substantial equivalence to separate Ohmeda – Ohio Care Plus Incubator, the Ohmeda – Ohio Infant Warmer System, and the Ohio Intensive Care Incubator. In the performance data section of the application it states, "Since the care of newborns in incubators and radiant warmers is a well-established clinical practice, Ohmeda submits that clinical or animal testing to demonstrate safety and effectiveness is

not necessary." Although it is a hybrid device, its equivalence was accepted and market access was granted (U.S. Food and Drug Administration, 2000).

The 510(k) clearance process based on substantial equivalence can be controversial with respect to patient safety, however, the system is in place to help manufacturers expedite the time it takes them to gain market access (Wizemann, 2010). Some experts believe that the FDA regulatory requirements are slow, risk-averse, and expensive compared to that of the European Union, while others believe that the process is not comprehensive enough. It is a debate that continues as global bodies continue to strive for harmonization between regulatory bodies (PricewaterhouseCoopers, 2011).

Once a medical device has gained market access in the U.S., medical device manufacturers must follow certain post-market requirements and regulations. Post-market requirements include such things as tracking systems, reporting of device malfunctions, reporting of serious injuries and death, and establishment registration where devices are manufactured or distributed. Under Section 522 of the FD&C, post-market regulation requirements also include post-market surveillance studies, as well as post-approval studies required at the time of a PMA approval or HDE application (U.S. Department of Health and Human Services, 2014). Establishment registration must happen annually.

Medical Device Regulation in the United Kingdom

The Medicines and Healthcare Products Regulatory Agency (MHRA) is an executive agency funded by the Department of Health and Social Care. The MHRA is the designated Competent Authority in the U.K. that regulates medical devices, medicines, and blood components for transfusion in the U.K. (Medicines & Healthcare products Regulatory Agency, 2017). It promotes and supports innovation while ensuring that health technologies meet required quality, safety, and efficacy standards. Medical Devices are regulated according to the Medical Device Regulations No. 618 (MDR) (as

amended in 2002) and the General Product Safety Regulations 2005 (SI 2005 No 1803) under the Consumer Protection Act of 1987 (World Health Organization, 2016).

In order to regulate the complex market in the European Union (EU) in the 1990s, three EU Directives were produced that outlined the requirements under which, if approved by a member state, a medical device can be marketed across the EU. The directive from 1993 outlined that regulatory approval by a regulatory authority or a Notified Body in the EU results in a device receiving a Conformité Européenne (CE) mark to show that the device has passed the conformity assessment (Kramer, Xu, & Kesselheim, 2012).

The main steps of acquiring a CE mark include, classifying the medical device, selecting the appropriate conformity assessment procedure for the Class of device, applying for certification from a notified body, ensuring the device complies with the defined essential requirements, establishing technical documentation, and issuing a declaration of conformity, and labelling the device with a CE marking (Wilson, 2010).

In the United Kingdom, devices are categorized into one of four classes, as seen in Table 9. Classes are designated based on increasing risks associated with their intended use (European Council, 1993; MHRA, 2017). Low-risk Class I devices that comply with the EU Medical Device Directive of 1993 (MDD) (amended in May 2017 with all changes to come into effect by 2020), must be declared to the MHRA which may ask for quality standard details before approving a CE mark (Department of Health and Social Care, 2016; The European Parliament and the Council of the European Union, 2017). Class IIa devices require a declaration of conformity to requirements listed in the MDD and the MDR. Manufacturers decide the appropriate assessment listed in the Annex of the MDD and apply for a CE. Class IIb devices, like the Giraffe Omni Bed, require more detailed documentation in addition to that required for a Class IIa device to receive a CE mark (Department of Health and Social Care, 2016). These assessments include performance and reliability testing related to their safety and intended use. A Class III device requires the most regulation to receive a CE mark from a notified body. Assessments may include

a design dossier examination and an audit of the full quality assurance system among other requirements (Department of Health and Social Care, 2016). Specific requirements for clinical studies are vague. The standard for most devices is reached if the manufacturer can prove that the benefits of a device outweigh the risk. Like regulation in Canada, devices must meet ISO standards (European Commission, 1993; Kramer, Xu, & Kesselheim, 2012).

Post-market surveillance by manufacturers is required in the U.K as in Canada and the U.S.. Adverse events that take place in the U.K. as a result of the use of a medical device, must also be reported to the MHRA. Since 2011, manufacturers of devices on the market in the EU are also required to report all adverse events (safety concerns) to the European Databank on Medical Devices (EUDAMED). EUDAMED stores information on medical device approvals, clinical studies, and post-market surveillance. While utility of the database is limited, it has proven useful with the coordination and analysis of post-marketing reports (Kramer, Xu, & Kesselheim, 2012).

6.4 Health Technology Assessment Worldwide

HTA is an important tool that supports a strong global health system (World Health Organization, 2011). As seen in the policy scan in this report, Canada, the United States and the United Kingdom all have well-developed health care systems that strive to use HTA and evidence-based medicine (EBM) to help inform important decisions around the regulation of health technologies and provision of health care services and their costs. Every country approaches HTA somewhat differently. There is no one model has been universally accepted, nor does it seem that one model that would work for all societies (O'Donnel, Pham, Pashos, & Miller, 2009). For the HTA process to be comprehensive, regardless of the health system that the technology is impacting, it should combine clinical effectiveness, economic evaluations, budget impact, societal values, and ethical considerations. While CADTH and NICE included most of these considerations, KPRA only considers an economic evaluation after a preliminary approval (Oortwijn W. , 2017).

Currently, there are many international organizations that aim to facilitate efficiencies, collaboration and knowledge-sharing in the sphere of EBM and HTA (Conference Board of Canada, 2017).

EUnetHTA is an organization that provides an effective and sustainable network for HTA across Europe. It aims to facilitate knowledge-sharing and good practices between agencies and countries. Some joint assessments have been undertaken through the network (EUnetHTA, 2018). Health Technology Assessment International (HTAi) is a global scientific and professional society with membership from 65 countries that shares information and expertise through the creation of papers, interest groups, and a policy forum. HTAi serves as a hub and provides a discussion platform for members on the efficient production and use of HTAs (HTAi, 2015). International Network of Agencies for Health Technology Assessment (INAHTA) is a network of 49 agencies around the world. INAHTA shares information about producing and disseminating HTA reports for evidence-based decision-making (INAHTA, 2018). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) is a professional society that advances the policy and practice of health economics and health outcomes research. ISPOR has an HTA council and hosts HTA roundtables (ISPOR, 2018).

Health systems are strengthened when HTA is integrated into transparent decision- and policy-making (World Health Organization, 2011). HTA is associated with an overall vision of equity and accountability within a health system. Good governance can rely on HTA to provide a policy approach that is accountable for its decisions to the population (World Health Organization, 2011).

HTAs must involve rigour and provide useful information for decision-makers. In turn, decision-makers must demonstrate a commitment to use the evidence reported and create policy frameworks that incentivize good practices (World Health Organization, 2011). Many HTA producers and international HTA organizations believe that creating a standardized methodological approach to the HTA of medical devices would be beneficial (Fuchs, Olberg, Panteli, & Busse, 2016).

All aforementioned organizations, and others, play an important role in the international landscape of HTA. In a global economy, optimizing HTA processes internationally would be efficient for industry, health care users, and health care providers. INAHTA provides various tools such as an HTA report checklist to promote a consistent and transparent approach to HTA (INAHTA Secretariat, 2007). Finding the optimal framework, utilization and implementation of HTA, understanding the best time within the life-cycle of a medical device to conduct and use it, and finding a way to make HTA relevant across jurisdictions could improve access to the best health care services available while also promoting fiscal responsibility.

6.4.1 Challenges with the HTA of Medical Devices

The medical device industry tends to focus on addressing long-term patient and health system needs. New medical innovations aim to address budgetary and human limitations. Medical devices can often offer long-term gains but can require significant investment up front from a health care provider as well as a manufacturer. One of the biggest issues facing medical device manufacturers is that significant short-term investments required from health care administrators often exceed short-term fiscal budgets (Tarricone, Torbica, & Drummond, 2017; Callea, Armeni, Marsilio, & Jommi, 2016).

Most HTA producers assess medical devices and pharmaceuticals using the same framework and considerations - a framework that was originally created to assess pharmaceuticals. Experts are increasingly realizing that HTA of medical devices requires special considerations and possibly its own framework (Ciani, et al., 2015). Major differences to consider when evaluating medical devices are: 1. Medical devices can continue to evolve as the device is diffused into the market. It is, therefore, important to find alternatives for a comparative and incremental cost-effectiveness analysis. 2. The interaction between a device and the healthcare professional using it can result in a learning-curve effect. The learning curve can affect data in safety and effectiveness

trials. 3. Medical devices have an organizational level impact due to the infrastructure they may require training that must take place when a new device is used in clinical practice. 4. There are often ethical issues to consider around treatment of a patient during a clinical trial. 5. The costing of medical devices requires a flexible approach. Pricing is dynamic and it is often difficult to get the full scope of the procurement costs (including training and infrastructure) and on-going costs (including maintenance and consumables) (Kirisits & Redekop, 2013; Tarricone, Torbica, & Drummond, 2017). As a result of these challenges, HTAs of medical devices are undertaken much less often than the HTA of drugs.

In Europe, a group of researchers undertook a project called the "MedtechHTA project" to investigate what sort of improvements need to be made to the HTA process to allow for a more comprehensive evaluation of medical devices (Tarricone, Torbica, & Drummond, 2017). The project is a collaboration between and among six European countries including the United Kingdom. HTA of medical devices is a dynamic field that many researchers and organizations continuously attempt to perfect.

HTA initiatives in Canada are dynamic, extensive and thorough. While HTA agencies are constantly adapting to changes in the health care system, challenges exist, particularly with respect to the HTA of medical devices (Polisena, 2017). With the ever-growing number of medical devices applying for market approval, selecting which devices are given priority for HTA is difficult. With the increasing complexity of many of these devices, HTA producers acknowledge that current processes may need to be further adapted and multiple stakeholders consulted (Henshall, Bayne, Frondsal, & Klemp, 2011). More input from patients, ethical considerations, and implementation issues are all important steps that should be included in the HTA of medical devices, however, the amount of time it takes to produce a report may increase and can, in turn, delay the time it takes a device to reach the market (Polisena, 2017; Conference Board of Canada, 2017). A balance must be found between creating reports to help with evidence-based decisions and giving manufacturers timely access to the market and patients access to the best medical innovations.

Procurement of any medical device that is over CAD $100 000 must have an open competitive bid process. Evaluation of the devices can be lengthy and is based on cost, patient outcomes, ease of use, and utility (Husereau, Arshoff, Bhimani, & Allen, 2015). Based on the price a Toronto hospital paid for the Giraffe Omni Bed in 2013 (CAD $71 300), it is inferred that the purchase of this device did not and would not have to follow this process in the future. The procurement and purchasing decision is up to the hospital administration in most provinces (Martin, Polisena, Dendukuri, Rhainds, & Sampietro-Colom, 2016). Hospital based HTA that uses a value framework to evaluate a new medical device is something that every institution should have to ensure a sound purchase.

6.4.2 Addressing the Lack of Clinical Evidence in Regulation and Health Technology Assessment

Regulatory bodies have the monumental task of ensuring patient safety while providing patients with the most innovative technology possible for treatment. The right balance of premarket assessment and post-market surveillance without compromising patient safety in the regulatory process is essential in providing patients with access to the best health care services possible (U.S. Department of Health and Human Services, 2015).

In many countries, medical devices are able to be used in clinical practice without clinical evidence (Tarricone, Torbica, & Drummond, 2017). In the United States, the FDA recognizes that there are risks associated with all medical devices that are on the market. At the time of premarket approval, all safety and effectiveness concerns may not have been fully addressed. The process is imperfect. Some experts have criticized the FDA for being slow and burdensome as many devices first become available for use in Europe, while other experts criticize the process stating that the level of evaluation required for clearance is insufficient (Resnic & Matheny, 2018). More regulations generally mean

more time until a device becomes available to patients and begins to make money for a manufacturer. Some manufacturers are required to conduct post-approval studies in order to provide more clinical evidence to regulatory authorities to receive on-going clearance.

The efficacy of a device is expected to vary in its effectiveness due to the learning curve with users of the device. Effectiveness studies result in evidence that demonstrates actual health care circumstances that, in turn, allows for more generalizable findings (Ferrusi, Ames, Lim, & Goeree, 2009). These studies can focus on a specific patient population or allow for the use of more than one intervention at a time and can only be conducted once a device has been approved for distribution.

There is a growing acceptance in the scientific community that under certain conditions, real-world studies that are based on real-world data (RWD) can provide useful evidence to researchers and decision-makers. These effectiveness studies are considered to be a fast and valuable source of information for technologies whose diffusion process has already begun (Tarricone, Boscolo, & Armeni, 2016). RWD could produce relevant evidence for economic evaluations and policy decisions such as reimbursement and coverage (Dreyer, Tunis, Berger, Ollendorf, Mattox, & Gliklich, 2010). Sources of observational RWD include databases (cross-sectional and longitudinal) that can provide data on quality of life, patient surveys for epidemiological information, patient chart reviews that can provide information about patient management (electronic medical records), insurance claims information, billing data, and clinical registries that prospectively collect information and then retrospectively analyze patient data (Annemans, Aristides, & Kubin, 2007; Resnic & Matheny, 2018).

Post-market controls such as surveillance of devices, adverse event reporting, and post-market studies are put in place to reduce premarket requirements and, in turn, get a device to market faster. Active post-market surveillance and the use of and the application of real-world evidence can improve a decision-maker's understanding of the performance of a medical device (Resnic & Matheny, 2018). Real world observational evidence can be used in several ways including: to evaluate and solve a post-market

regulatory issue such as a reclassification of a device, the expansion of labelling of a device and its updated indications for use, and to conduct post-approval studies that were imposed as a condition of a device approval (U.S. Food & Drug Administration, 2017). It can also help decision-makers to better understand which population of patients benefits the most from a particular medical device. RWD used in a study must include sufficient details on the use of the device and the outcomes of interest for the appropriate population. The study design and protocol must be appropriate to address the regulatory question at hand in a timely manner (Tarricone R. , Torbica, Ferre, & Drummond, 2014).

RCTs, the gold standard for clinical evidence, are time-consuming and expensive and manufacturers generally only work to fulfill the minimal evidence requirements needed to gain market access (Ferrusi, Ames, Lim, & Goeree, 2009). Comparative RCTs, if required, are often done after the diffusion process has begun and often require quite a lot of time. In the meantime, RWD can be collected and assessed for evidence to use in recommendations to decision-makers. This information can be especially helpful in patient treatment-pathway considerations, coverage, reimbursement and procurement choices (Tarricone, Boscolo, & Armeni, 2016).

As a result of the lack of evidentiary requirements in the regulation process of a medical device, the evidence needed to conduct a thorough HTA of that device is often inadequate (Lamph, 2012; Conference Board of Canada, 2017). The use of observational studies, produced from RWD as clinical evidence for a HTA, is gaining international recognition (Tarricone, Boscolo, & Armeni, 2016).

As stated, the HTA of medical devices generally takes place after the diffusion of a device has begun. As such, HTA producers and decision-makers cannot ignore that some patients, health care professionals, and organizations are already familiar with the device (Tarricone, Boscolo, & Armeni, 2016). Understanding all the challenges around evidence generation for medical devices, some decision-makers are willing to share the risk and financial investment involved in conducting effectiveness studies in a real-world setting (Ferrusi, Ames, Lim, & Goeree, 2009; Tarricone, Boscolo, & Armeni, 2016).

Some decision-makers will allow for adoption of a device into their health care system or institution with the understanding that more clinical evidence will be produced and provided to them in a timely manner. This collaborative approach results in a lesser financial burden on the manufacturer (Conference Board of Canada, 2017).

Health outcomes for medical devices greatly rely on the end-user's experience. Clinical evidence available for devices can vary due to differences in the training, the skill-level and the experiences of the healthcare providers using the devices (Tarricone R. , Torbica, Ferre, & Drummond, 2014). These real-world factors are important to consider in the production of clinical evidence, and real-world observational studies can account for this.

Researchers involved in the MedtechHTA project believe that if RWD are robustly analyzed and elaborated on, the evidence produced can inform decision-making, and is especially useful if the alternative would be to not allow end-users to use the innovation (Tarricone, Boscolo, & Armeni, 2016). However, not all health outcome and health economics researchers agree. A real-world cost-effectiveness analysis (CEA) on the MitraClip, an implantable device that allows a fully percutaneous approach to mitral regurgitation, produced in 2016, was met with a lot of controversy (Armeni, et al., 2016). The scientific community reviewed this economic evaluation negatively and believed that a CEA is only reliable if it is based on experimental evidence. They did, however, agree that for policy decisions like coverage and reimbursement, observational real-world studies are just as relevant, if not more relevant, than experimental study designs.

The greatest concern in using these real-world studies is selection bias. The allocation of patients to either the control or treatment group can be based on their baseline characteristics or factors like clinical knowledge of the medical professional treating the patient. The bias can be measured and reported. Tools like multivariate regression and nonparametric techniques based on a propensity score are used to address some of the selection bias concerns (Tarricone, Boscolo, & Armeni, 2016).

Real world observational studies that are methodologically sound address challenges of conducting RCTs with medical devices by factoring in the learning curve, cheaper and easier data collection, fewer ethical issues, and are potentially timelier (Tarricone, Boscolo, & Armeni, 2016). If economic evaluations, HTAs and policy recommendations are not done in a timely manner, there is a risk that they will be ineffective or irrelevant once they are produced as the device may already be fully diffused into clinical practice.

The study by Kim et al. in this review is a retrospective observational study. The data used in the study were sourced from patient records. Mixed design, linear and non-linear multiple regression models were used to determine factors associated with outcome measurements. Primary and secondary outcomes were analyzed using binary logistic regression, linear regression, and Poisson regression models that were adjusted for multiple births using SPSS. Through the Newcastle-Ottawa Scale, the study was determined to be of a moderate risk of bias. If real-world studies continue to gain respect as reliable sources for clinical evidence in economic evaluations and HTAs, it could be a game-changer for regulatory bodies and manufacturers. More methodologically sound; comparative studies such as the one by Kim et al. on the Giraffe OmniBed could prove to be extremely useful information to manufacturers and decision-makers with respect to production of a full HTA and the future procurement and purchasing of the Giraffe OmniBed and similar devices.

6.4.3 Key Findings from Policy Scan

Canada, the United States and the United Kingdom all have varying levels of premarket and post-market regulations for medical devices. The ongoing debate around medical device regulation is often based around the amount of clinical evidence required. As seen, requirements vary greatly across jurisdictions. Regulation requirements and the quality of evidence needed to conduct an HTA are not well-aligned with the standard life-cycle of a medical device. (Ferrusi, Ames, Lim, & Goeree, 2009).

While regulatory and HTA framework policies share many of the same principles, differences exist between and among jurisdictions. Canada, the United States, and the United Kingdom all have their own national regulatory authorities that are responsible for carrying out regulatory activities in their respective countries. Each country has an explicit definition of a medical device, a detailed device classification system, essential safety and performance requirements, conformity assessment bodies, manufacturer establishment registration requirements, adverse event reporting, assessment of non-compliance, and recall systems in place. While the classification of devices in all countries is based on level of risk and intended use of the medical devices, classification and regulatory requirements for each Class varies among countries.

In Canada, the U.S. and the U.K., the more high-risk a device is classified, the more information is required about the safety and effectiveness of that device before it reaches the market. Even still, most medical devices often make it to market with a limited amount of safety and efficacy data that can be obtained from small-scale studies (Henshall, Bayne, Frondsal, & Klemp, 2011; Conference Board of Canada, 2017). Researchers are attempting to address this information gap by evaluating devices and evidence after a device has already received market access and incorporating the research into post-market regulatory processes.

Various value frameworks have been and continue to be created by various agencies in all three countries to help decision-makers better understand the value of a device and if it deserves their finite resources. Differences seen in the policy scan results show just how much value frameworks can differ between agency and jurisdiction. Particularly notable is the value framework produced by the Medical Device Innovation Consortium (MDIC) that is intended to improve the understanding of the FDA and sponsors on how patient preferences with respect to benefit and risk might be incorporated into the regulatory review process for innovative medical devices. This is a new progressive approach being created to facilitate cohesion between the regulatory process and evidence-based decision making (Medical Device Innovation Consortium, 2015).

Decision-makers and regulatory agencies struggle to find the right balance between providing patients with fast access to innovative health technologies while also ensuring a safe product. Canada, The United States and the United Kingdom all have different approaches to address this issue for devices like the Giraffe OmniBed that present a medium level of risk. While Canada's regulatory process has many protocols in place to protect patient safety, it tends to drag out and take longer for medical devices to reach patients. The United States, on the other hand, with the less rigorous 510(k) process, has the ability to provide patients with access to devices in a more timely manner. This also means faster market access to manufacturers who want to start making returns on their investment. Regulation in the United Kingdom, on the other hand, with the use of Notified Bodies, CE marks, and Competent Authorities in the EU seems to have found more of a balance with respect to time and rigour. These policies, however, have resulted in a lack of evidence generation for devices like the Giraffe OmniBed.

6.5 Implications of Findings and Ethical Considerations

The care of ELBW preterm infants is expensive and complex. This thesis systematically compiled all available comparative research on the effectiveness, efficacy and/or safety of the Giraffe OmniBed as its primary objective. The secondary objective of this review was to scan and compare medical device regulation policies and national health technology assessment value frameworks in Canada, the U.S. and the U.K. There are implications in the findings for various stake holders, including, decision-makers, institutions, health care providers, and families.

Institutions have finite budgets and infrastructure and their costs and space need to be allotted with great care. NICUs have long been considered controversial due to the extremely high costs associated with them. Is the price worth the expenditure? What is the evidence? The Giraffe OmniBed is one of many expensive devices found in a NICU. Which devices should limited resources be allocated to and why? Those responsible for budgeting within a hospital have an ethical and fiduciary responsibility to make evidence-based decisions. Once the decision is made to intervene with an ELBW preterm infant in

a life-saving way, providing the best intervention possible is the only ethical choice. While this review suggests that there may be improved outcomes for infants cared for in a Giraffe OmniBed, it cannot be concluded with certainty due to the scarcity of evidence and the very low quality evidence found.

This review highlights the lack of clinical evidence available for the Giraffe OmniBed and other similar devices. At the same time, it highlights the challenges in gathering evidence to support the responsible purchase of medical devices. Challenges of evidence generation for medical devices include the ethical considerations of randomizing a patient to a particular intervention, the lack of blinding involved for the researcher, and the learning-curve that healthcare professionals experience when they first start using a device. Decision-makers at a global, national, regional, and local-level who create policy within their respective public health system need evidence-based recommendations from comprehensive HTA reports to make thoughtful and transparent choices around the diffusion of medical devices. Policy-makers should continue to examine their interactions with industry and lobby for improved evidence generation in the interest of better patient safety. They should also continue to broaden their horizons with respect to the type of evidence they consider "good" enough for further synthesis. RWD may be a good alternative to determine the effectiveness, efficacy, and/or safety of the Giraffe OmniBed and similar devices.

If further research confirms that both short-term and long-term outcomes are indeed better for ELBW preterm infants treated in a Giraffe OmniBed, then healthcare professionals should employ these devices when treating ELBW preterm infants whenever possible. If ELBW preterm newborns do not receive optimal care at the beginning of their lives, increased morbidities can cause lifelong health struggles and significantly add to health care and related costs later in life. These costs could include personalized interventions like special education, specialized equipment, speech therapy, physiotherapy, and occupational therapy. It is in the decision-makers' interests to minimize morbidities and, in turn, minimize the impact of preterm birth on society.

The financial obligations related to premature births and their consequences are assumed by individuals, families, employers, and ultimately society even in countries like Canada and the U.K. with access to universal health care for all their residents. Whether paid directly by individual families, insurance companies, taxpayers and/or employers through healthcare premiums in countries like the U.S., the costs are significant, and extend beyond direct costs (Petrou, Henderson, Bracewell, Hockley, Wolke, & Marlow, 2006). This can cause a great deal of financial and emotional stress to the families of the premature baby.

Regulatory agencies and HTA agencies should work to coordinate their efforts on an international level in the interest of patient safety and efficiency of care. Presently there is a lack of consistency in the regulation of medical devices and the value frameworks used to assess them across and between jurisdictions and HTA agencies. Inconsistencies in regulations make the job of a manufacturer trying to gain access to different international markets much more difficult and lengthy. Inconsistencies in the value frameworks used by HTA agencies can result in different funding recommendations for the same devices and, in turn, a lack of equity in patient care and patient access across jurisdictions. While efforts are underway globally to harmonize regulatory requirements and value frameworks for medical devices in high-income countries, better collaboration among regulatory authorities, HTA agencies, and coverage bodies could have a positive impact on budgets, ease of procurement, and patient care.

Table 13: Hybrid Incubator/Radiant Warmer Devices

	Giraffe OmniBed[9][10]	**Versalet 7700 Care System**	**Dual incu *i***	**Babyleo TN500 -2017**
Description	Hybrid Incubator and Radiant Warmer	Hybrid Incubator and Radiant Warmer	Hybrid Incubator and Radiant Warmer	Hybrid Incubator and Radiant Warmer
Manufacturer	Ohmeda Medical, A Division of Datex, a GE Company	Hill-Rom, Air Shields	Atom Medical Corporation	Draegerwerk AG & Co. KGaA
Year to Market	2000 (USA) 2000 (CANADA)	2001 (USA) 2001 (CANADA)	2011 (USA) 2015 (CANADA)	2017 (USA) 2017 (CANADA)
Class of device	Class III (TPD) Class II (FDA) Class IIb (MHRA)	Class III (TPD) Class II (FDA) Class IIb (MHRA)	Class III (TPD) Class II (FDA) Class IIb (MHRA)	Class III (TPD) Class II (FDA) Class IIb (MHRA)
Newest Version of Device by Manufacturer	Giraffe OmniBed Care-station - 2015	No longer in production. Air Sheids was bought out by Draeger Device license end date: 11/2009 (CANADA)	This is the newest generation of the devices offered by the manufacturer.	This is the first incubator-warmer hybrid that Drager has produced.

[9] Information on all of the devices in the USA market was found on the U. S. Food and Drug Administration website (www.fda.gov)

[10] Information on all of the devices in the Canadian market was found on the in the Government of Canada Medial Device Active License listing (https://health-products.canada.ca)

7.0 Conclusion

The care of preterm infants is a complex and expensive undertaking and health care resources are finite. Resources must be allocated responsibly through a methodical and transparent process. When a new medical device applies for market clearance, it is the job of regulatory agencies worldwide to ensure that the device is safe and functions at a high level. ELBW preterm infants are not able to speak for themselves; it is the ethical responsibility of policy-makers and decision-makers to provide them with access to the best care possible.

The Giraffe OmniBed entered the market in the United States and Canada in 2000 and has been steadily diffusing through health care systems worldwide. This literature review set out to systematically locate, review, and analyze original studies and to summarize comparative evidence about the effectiveness, efficacy and safety of the Giraffe OmniBed as assessed by physiological indicators (body temperature, body weight, fluid and electrolyte balance).

Strategic searches of MEDLINE, EMBASE, Google Scholar, HTA databases, references, and grey literature were conducted and two retrospective observational studies that evaluated the effectiveness and safety of the Giraffe OmniBed were identified for inclusion. The risk of bias across studies was assessed using the GRADE approach. Evidence on skin maturity, body temperature, growth, and episodes of hypothermia was of very low quality. While the literature reviewed suggests that the Giraffe OmniBed could be better than conventional incubators in maintaining thermal stability, improving skin maturity and growth outcomes for ELBW preterm infants, it cannot be stated with confidence due to the very low quality of the included evidence that was not suitable to statistical synthesis. Researchers should use this study as a benchmark to continue future research. While there are ethical considerations around including ELBW preterm infants

into randomized controlled trials, more real world observational studies, both prospective and retrospective, could serve as a good starting point to grow the body of evidence.

This review highlighted that the lack of evidence available for the Giraffe OmniBed is true for most medical devices that carry the same level of risk. A policy scan of regulation of medical devices in Canada, the United States and the United Kingdom demonstrated that regulation approval for devices, while lengthy, does not actually require a great deal of comparative clinical evidence. This paucity of evidence makes it very difficult for health outcomes researchers to access necessary information on outcomes of interest for further synthesis. The generation of high quality clinical evidence takes a lot of time. Once a medical device has been innovated, the manufacturer has very little time to get it to market before another version of the device comes out. Without high quality evidence, researchers are not able to satisfy the comprehensive requirements of HTA value frameworks that provide guidance and recommendations to decision-makers on allocation of resources. Informed and transparent procurement of medical devices is essential, however, regulatory processes do not lend themselves to evidence generation and, therefore, does not lend themselves to informed decision making through HTA.

Informed decisions around the allocation of resources thorough health technology assessment of medical devices using value frameworks are crucial components of sustainable high quality healthcare.

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Appendix 1: Electronic Search Strategy - MEDLINE

MEDLINE	1	("Giraffe* bed*" or Giraffebed* or "Giraffe-bed*" or "Giraffe* omnibed*" or "Giraffe* omni-bed*" or "hybrid humidified incubator*" or "hybrid microenvironment* device*").ti,ab.
	2	Incubators, Infant/ or ((infan* or neonat* or newborn* or prematur* or preemie* or ELBW) adj3 (warmer* or radiant or incubator*)).ti,ab. or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, premature/ or infant, extremely premature/ or intesive care, neonatal/ or intensive care units, neonatal/ or neonatal nursing/
	3	body temperature/ or body temperature regulation/ or thermogenesis/ or shivering/ or skin temperature/ or body temperature changes/ or fever/ or hypothermia/ or temperature/ or hot temperature/ or transition temperature/ or humidity/ or life support systems/ or ventilation/ [****primary outcome terms****]
	4	("clinical trial, all" or clinical trial).pt. or clinical trials as topic/ or clinical trial, phase i.pt. or clinical trials, phase i as topic/ or clinical trial, phase ii.pt. or clinical trials, phase ii as topic/ or clinical trial, phase iii.pt. or clinical trials, phase iii as topic/ or clinical trial, phase iv.pt. or clinical trials, phase iv as topic/ or controlled clinical trial.pt. or controlled clinical trials as topic/ or meta-analysis.pt. or meta-analysis as topic/ or multicenter study.pt. or multicenter studies as topic/ or randomized controlled trial.pt. or randomized controlled trials as topic/
	5	2 and 3 and 4 [****primary outcome results****]
	6	body weight/ or body weight changes/ or weight gain/ or weight loss/ [****secondary outcome****]
	7	2 and 4 and 6 [****secondary outcome weight gain results****]
	8	7 not 5 [****duplicates removed secondary outcome weight gain results****]
	9	(skin adj2 (matur* or immatur*)).ti,ab. or skin physiological phenomena/ or skin physiological processes/ or skin absorption/ or skin/ or dermis/ or epidermis/ [****secondary outcome skin maturity****]
	10	2 and 4 and 9 [****secondary outcome skin maturity results****]
	11	10 not (5 or 7) [****duplicates removed secondary outcome skin maturity results****]
	12	water-electrolyte balance/ or kallikrein-kinin system/ or water loss, insensible/ or exp Water-Electrolyte Imbalance/ [****secondary outcome electrolyte balance****]
	13	2 and 4 and 12 [****secondary outcome electrolyte balance results****]
	14	13 not (5 or 7 or 10) [****duplicates removed secondary outcome electrolyte balance results****]
	15	1 or 5 or 7 or 10 or 13
	16	limit 15 to latest update [limit ignored during autoalert processing]

Appendix 2: Electronic Search Strategy – EMBASE

EMBASE	1	("Giraffe* bed*" or Giraffebed* or "Giraffe-bed*" or "Giraffe* omnibed*" or "Giraffe* omni-bed*" or "hybrid humidified incubator*" or "hybrid microenvironment* device*").ti,ab.
	2	incubator/ or ((infan* or neonat* or newborn* or prematur* or preemie* or ELBW) adj3 (warmer* or radiant or incubator*)).ti,ab. or low birth weight/ or extremely low birth weight/ or small for date infant/ or very low birth weight/ or prematurity/ or newborn intensive care/ or newborn intensive care nursing/ or nicu*.ti,ab.
	3	body temperature/ or rectum temperature/ or body temperature disorder/ or accidental hypothermia/ or chill/ or cold clammy skin/ or fever/ or hyperpyrexia/ or hyperthermia/ or hypothermia/ or shivering/ or thermoregulation/ or temperature acclimatization/ or humidity/ or moisture/ or microclimate/ or air conditioning/ or exp humidifier/ or indoor air pollution/ or room ventilation/ or workroom air/ or skin temperature/ or temperature/ [****primary outcome terms****]
	4	ct.fs. or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or crossover procedure/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or (rct or rcts or random* or ((single or double or tripl*) adj2 (mask* or blind* or trial*)) or (clinical adj5 trial*)).ti,ab. or multicenter study/ or (multicentre adj2 (analys* or study or studies)).ti,ab. or (multicenter adj2 (analys* or study or studies)).ti,ab. or meta analysis/ or (Metaanalys* or "meta-analys*").ti,ab. [****Sensitive Therapy Quality filtering terms - 1947 to present****]
	5	2 and 3 and 4 [****primary outcome results****]
	6	body weight/ or birth weight/ or liveweight gain/ or weight change/ or weight control/ or weight fluctuation/ or weight gain/ or weight reduction/ [****secondary outcome****]
	7	2 and 3 and 6 [****secondary outcome weight gain results****]
	8	5 not 7 [****duplicates removed secondary outcome weight gain results****]
	9	(skin adj2 (matur* or immatur*)).ti,ab. or "functions of the skin and its appendages"/ or skin conductance/ or exp skin function/ or skin penetration/ or skin permeability/ or skin sensitivity/ or skin sensitization/ or skin/ or exp dermis/ or exp epidermis/ [****secondary outcome skin maturity****]
	10	2 and 3 and 9 [****secondary outcome skin maturity results****]
	11	10 not (5 or 7) [****duplicates removed secondary outcome skin maturity results****]
	12	metabolic balance/ or acid base balance/ or exp electrolyte balance/ or fluid balance/ or kallikrein kinin system/ or (insensible adj2 (fluid* or water) adj2 loss*).ti,ab. or (Water adj2 Electrolyte adj2 Imbalance).ti,ab. [****secondary outcome electrolyte balance****]
	13	2 and 3 and 12 [****secondary outcome electrolyte balance results****]
	14	13 not (5 or 7 or 10) [****duplicates removed secondary outcome electrolyte balance results****]
	15	1 or 5 or 7 or 10 or 13
	16	limit 15 to latest update [limit ignored during autoalert processing]

Appendix 3: Search Strategies – Google Scholar, CADTH Grey Matters and References

Search term in Google Scholar:
"Giraffe OmniBed"
"Giraffe Omni-Bed"
"OmniBed"
"Omni-Bed"
"Giraffe Carestation"
"Hybrid Humidified Incubator"

CADTH Grey Matters Checklist Results	
Search Engine	**Number of hits**
Irish Health Repository **(**Lenus**)** http://www.lenus.ie/hse/	6
NHS Purchasing and Supply Agency Centre for Evidence-based Purchasing (CEP) http://nhscep.useconnect.co.uk/CEPProducts/Catalogue.aspx	5
ECRI Institute http://www.ecri.org/ (subscription required)	10
Health Canada. Devices Medical Devices Active License Listing (MDALL) http://webprod5.hc-sc.gc.ca/mdll-limh/index-eng.jsp	6
US Food and Drug Administration (FDA) Devices http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm	4
Health Canada. Healthy Canadians- Search recalls and safety alerts http://healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php	6

Reference Search Strategy:
1. The full-text of any study that mentioned the Giraffe OmniBed was pulled.
2. Studies were read for possible information on relevant outcomes.
3. Any information provided by the study that was identified as possible useful had the reference checked.
4. All references were scanned for any titles that were clearly about a Giraffe OmniBed or a hybrid humidified incubator.
5. Any relevant studies found in the references were pulled and the full-text was read.

Appendix 4: Included and Excluded Studies after Full-text Review

Author s	**Year**	**Publication Title**	**Include/Exclude**	**Reason for Exclusion**
Bastug, O.; Gunes, T.; Korkmaz, L.; Elmali, F.; Kucuk, F.; Ozturk, M. A.; Kurtoglu, S.	2016	An evaluation of intra-hospital transport outcomes from tertiary neonatal intensive care unit	Exclude	inappropriate intervention
Bhatt, R.; Alexandra, P.; Patel, D.; D'Costa, W.; Chuang, S. L.	2016	Evaluation of early stabilisation of extremely preterm infants (EPI) in the delivery room and neonatal-intensive-care-unit (NICU)	Exclude	inappropriate intervention
Duryea, E. L.; Nelson, D. B.; Wyckoff, M. H.; Grant, E. N.; Tao, W.; Sadana, N.; Chalak, L. F.; McIntire, D. D.; Leveno, K. J.	2016	The impact of ambient operating room temperature on neonatal and maternal hypothermia and associated morbidities: A randomized controlled trial	Exclude	inappropriate intervention
Feldman, A.; De Benedictis, B.; Alpan, G.; La Gamma, E. F.; Kase, J.	2016	Morbidity and mortality associated with rewarming hypothermic very low birth weight infants	Exclude	inappropriate intervention
Mank, A. V.; Van Zanten, H. A.; Meyer, M. P.; Pauws, S.; Lopriore, E.; Te Pas, A. B.	2016	Hypothermia in preterm infants in the first hours after birth: Occurrence, course and risk factors		inappropriate intervention
Mank, A.; Van Zanten, H. A.; Meyer, M. P.; Pauws, S.; Lopriore, E.; Te Pas, A. B.	2016	Hypothermia in preterm infants in the first hours after birth: Occurrence, course and risk factors	Exclude	inappropriate intervention
McGrory, L.; Kamlin, C. O. F.; Owen, L. S.; Dawson, J. A.; Rafferty, A. R.; O'Shea, J. E.; Roberts, C. T.; Donath, S. M.; Malhotra, A.; Davis, P. G.	2016	A comparison of humidified and unconditioned gases in the delivery room for stabilising preterm infants less than 30 weeks gestation: the humid study	Exclude	inappropriate intervention
Reynolds, P.; Leontiadi, S.; Lawson, T.; Otunla, T.; Ejiwumi, O.; Holland, N.	2016	Stabilisation of premature infants in the delivery room with nasal high flow	Exclude	inappropriate intervention
Shaw, A.; Jones, K.; Farooq, S.; Ashton, C.; Stevens, R.; Hopley, C.; Miall, L.	2016	Quality improvement project: Preventing hypothermia in neonates in a tertiary neonatal unit	Exclude	inappropriate intervention
Sim, M. A.; Leow, S. Y.; Hao, Y.; Yeo, C. L.	2016	A practical comparison of temporal artery thermometry and axillary thermometry in neonates under different environments	Exclude	inappropriate intervention

Swarnkar, K.; Vagha, J.	2016	Effect of kangaroo mother care on growth and morbidity pattern in low birth weight infants	Exclude	inappropriate intervention
Wlodaver, A.; Blunt, M.; Satnes, K.; Escobedo, M.; Hallford, G.; Szyld, E.	2016	A retrospective comparison of VLBW outcomes before and after implementing new delivery room guidelines at a regional tertiary care center	Exclude	inappropriate intervention
Amadi, H. O.; Olateju, E. K.; Alabi, P.; Kawuwa, M. B.; Ibadin, M. O.; Osibogun, A. O.	2015	Neonatal hyperthermia and thermal stress in low- and middle-income countries: a hidden cause of death in extremely low-birthweight neonates	Exclude	inappropriate intervention
Degorre, C.; Decima, P.; Degrugilliers, L.; Ghyselen, L.; Bach, V.; Libert, J. P.; Tourneux, P.	2015	A mean body temperature of 37degreeC for incubated preterm infants is associated with lower energy costs in the first 11 days of life	Exclude	inappropriate intervention
Degorre, C.; Decima, P.; Degrugilliers, L.; Ghyselen, L.; Bach, V.; Libert, J. P.; Tourneux, P.	2015	A mean body temperature of 37degreeC for incubated preterm infants is associated with lower energy costs in the first 11 days of life	Exclude	inappropriate intervention
Dehghani, K.; Movahed, Z. P.; Dehghani, H.; Nasiriani, K.	2015	A randomized controlled trial of kangaroo mother care versus conventional method on vital signs and arterial oxygen saturation rate in newborns who were hospitalized in neonatal intensive care unit	Exclude	inappropriate intervention
Hoffman, L.; Santos, M. A.; Tucker, R.; Laptook, A.	2015	Neonatal oesophageal and axilla temperatures in the neonatal intensive care unit care	Exclude	inappropriate intervention
Longhini, F.; Jourdain, G.; Ammar, F.; Mokthari, M.; Boithias, C.; Romain, O.; Letamendia, E.; Tissieres, P.; Chabernaud, J. L.; De Luca, D.	2015	Outcomes of preterm neonates transferred between tertiary perinatal centers	Exclude	inappropriate intervention
Longhini, F.; Jourdain, G.; Ammar, F.; Mokthari, M.; Boithias, C.; Romain, O.; Letamendia, E.; Tissieres, P.; Chabernaud, J. L.; De Luca, D.	2015	Outcomes of preterm neonates transferred between tertiary perinatal centers	Exclude	inappropriate intervention

Lyu, Y.; Shah, P. S.; Ye, X. Y.; Warre, R.; Piedboeuf, B.; Deshpandey, A.; Lee, S. K.; Harrison, A.; Synnes, A.; Sokoran, T.; Yee, W.; Aziz, K.; Kalapesi, Z.; Sankaran, K.; Seshia, M.; Alvaro, R.; Shivananda, S.; Da Silva, O.; Nwaesei, C.; Lee, K. S.; Dunn, M.; Rouvinez-Bouali, N.; Dow, K.; Pelausa, E.; Barrington, K.; Drolet, C.; Riley, P.; Bertelle, V.; Canning, R.; Bulleid, B.; Ojah, C.; Monterrosa, L.; Afifi, J.; Kajetanowicz, A.	2015	Association between admission temperature and mortality and major morbidity in preterm infants born at fewer than 33weeks' gestation	Exclude	inappropriate intervention
Meyer, M. P.; Hou, D.; Ishrar, N. N.; Dito, I.; Te Pas, A. B.	2015	Initial respiratory support with cold, dry gas versus heated humidified gas and admission temperature of preterm infants	Exclude	inappropriate intervention
Ogunlesi, T.	2015	Mortality within the first 24 hours of admission among neonates aged less than 24 hours in a special care baby unit (SBCU) in Nigeria: The role of significant hypothermia and hypoglycemia	Exclude	inappropriate intervention
Reilly, M. C.; Vohra, S.; Rac, V. E.; Dunn, M.; Ferrelli, K.; Kiss, A.; Vincer, M.; Wimmer, J.; Zayack, D.; Soll, R. F.	2015	Randomized trial of occlusive wrap for heat loss prevention in preterm infants	Exclude	inappropriate intervention
Romanzeira, J. C. F.; Sarinho, S. W.	2015	Quality Assessment of Neonatal Transport performed by the Mobile Emergency Medical Services (SAMU)	Exclude	inappropriate intervention
Rosin, M.; Ehrlich, L.; Margaret, B.	2015	Transporting neonates to the NICU: A comparative study	Exclude	inappropriate intervention
Saugstad, O. D.	2015	Delivery room management of term and preterm newly born infants	Exclude	
Skiold, B.; Stewart, M.; Theda, C.	2015	Predictors of unfavorable thermal outcome during newborn emergency retrievals	Exclude	inappropriate intervention
Zhou, W.; Yu, J.; Wu, Y.; Zhang, H.	2015	Hypoglycemia incidence and risk factors assessment in hospitalized neonates	Exclude	inappropriate intervention

AlKharfy, T.; Ba-Abbad, R.; Hadi, A.; AlFaleh, K.	2014	Use of topical petroleum jelly for prevention of sepsis in very low-birthweight infants: A prospective, randomised controlled trial	Exclude	inappropriate intervention
Arora, P.; Bajaj, M.; Natarajan, G.; Arora, N. P.; Kalra, V. K.; Zidan, M.; Shankaran, S.	2014	Impact of interhospital transport on the physiologic status of very low-birth-weight infants	Exclude	inappropriate intervention
Barrington, K. J.	2014	Management during the first 72 h of age of the periviable infant: an evidence-based review	Exclude	inappropriate intervention
Berger, I.; Marom, R.; Mimouni, F.; Kopelovich, R.; Dollberg, S.	2014	Weight at weaning of preterm infants from incubator to bassinet: a randomized clinical trial	Exclude	inappropriate intervention
Chitanda, D.; Wallace, E.; Jackson, P.; Shaikh, Z. H.	2014	Successful mitigation of a potential pseudomonas aeruginosa (PA) outbreak in a neonatal intensive care unit (NICU)	Exclude	inappropriate intervention
De Almeida, M. F. B.; Guinsburg, R.; Sancho, G. A.; Rosa, I. R. M.; Lamy, Z. C.; Martinez, F. E.; Da Silva, R. P. G. V. C.; Ferrari, L. S. L.; De Souza Rugolo, L. M. S.; Abdallah, V. O. S.; Silveira, R. D. C.	2014	Hypothermia and early neonatal mortality in preterm infants	Exclude	inappropriate intervention
Hsu, K. H.; Chiang, M. C.	2014	A randomised trial of using thermal blanket to improve thermoregulation among preterm infants	Exclude	inappropriate intervention
Jost, K.; Pramana, I.; Ramelli, V.; Delgado-Eckert, E.; Frey, U.; Schulzke, S. M.	2014	Temperature regulation in preterm infants-a prospective observational study	Exclude	inappropriate intervention
Kong, X. Y.; Liu, X. X.; Hong, X. Y.; Liu, J.; Li, Q. P.; Feng, Z. C.	2014	Improved outcomes of transported neonates in Beijing: the impact of strategic changes in perinatal and regional neonatal transport network services	Exclude	inappropriate intervention
Lee, H. C.; Bennett, M.; Powers, R.; Sharek, P.	2014	Collaborative vs individual quality improvement for delivery room neonatal management	Exclude	inappropriate intervention
McGrory, L.; Kamlin, C. O. F.; Owen, L. S.; Dawson, J. A.; Davis, P. G.	2014	A ten year review of delivery room management of preterm infants born between 25 and 28 weeks gestation in a tertiary neonatal centre	Exclude	inappropriate intervention
Schafer, D.; Boogaart, S.; Johnson, L.; Keezel, C.; Ruperts, L.; Van Der Laan, K. J.	2014	Comparison of neonatal skin sensor temperatures with axillary temperature	Exclude	inappropriate intervention

Schmolzer, G. M.; Pinson, R.; Molesky, M.; Chinnery, H.; Foss, K.; Cheung, P. Y.	2014	Temperature maintenance and oxygen use in newborns at birth: A surveillance of clinical practice and compliance with neonatal resuscitation guidelines	Exclude	inappropriate intervention
Akter, S.; Parvin, R.; Yasmeen, B. H. N.	2013	Admission hypothermia among neonates presented to Neonatal intensive care unit	Exclude	inappropriate intervention
Bellini, C.; Risso, F. M.; Serveli, S.; Natalizia, A. R.; Ramenghi, L. A.	2013	Simultaneous transport of twin newborns	Exclude	inappropriate intervention
Chen, L. C.; Wu, Y. C.; Hsieh, W. S.; Hsu, C. H.; Leng, C. H.; Chen, W. J.; Chiu, N. C.; Lee, W. T.; Yang, M. C.; Fang, L. J.; Hsu, H. C.; Jeng, S. F.	2013	The effect of in-hospital developmental care on neonatal morbidity, growth and development of preterm Taiwanese infants: a randomized controlled trial	Exclude	inappropriate intervention
Chitty, J.; Wyllie, J.	2013	Importance of maintaining the newly born temperature in the normal range from delivery to admission	Exclude	inappropriate intervention
Decima, P.; Bodin, E.; Chardon, K.; Stephan-Blanchard, E.; Delanaud, S.; Telliez, F.; Tourneux, P.; Andre, L.; Libert, J.; Bach, V.	2013	Skin temperatures and peripheral vasomotor control and sleep stages in preterm neonates	Exclude	inappropriate intervention
Heimann, K.; Ebert, A. M.; Abbas, A. K.; Heussen, N.; Leonhardt, S.; Orlikowsky, T.	2013	Thermoregulation of Premature Infants during and after Skin-to-Skin Care	Exclude	inappropriate intervention
Heimann, K.; Jergus, K.; Abbas, A. K.; Heussen, N.; Leonhardt, S.; Orlikowsky, T.	2013	Infrared thermography for detailed registration of thermoregulation in premature infants	Exclude	inappropriate intervention
Kumar, J.; Upadhyay, A.; Dwivedi, A. K.; Gothwal, S.; Jaiswal, V.; Aggarwal, S.	2013	Effect of oil massage on growth in preterm neonates less than 1800 g: a randomized control trial	Exclude	inappropriate intervention
McCarthy, L. K.; Molloy, E. J.; Twomey, A. R.; Murphy, J. F. A.; O'Donnell, C. P. F.	2013	A randomized trial of exothermic mattresses for preterm newborns in polyethylene bags	Exclude	inappropriate intervention
McGrory, L.; Dawson, J.; Owen, L.; Davis, P.	2013	Heating and humidifying gases for newborn resuscitation: A review of the literature	Exclude	inappropriate intervention
Sung, S. I.; Ahn, S. Y.; Seo, H. J.; Yoo, H. S.; Han, Y. M.; Lee, M. S.; Chang, Y. S.; Park, W. S.	2013	Insensible water loss during the first week of life of extremely low birth weight infants less than 25 gestational weeks under high humidification	Exclude	non-comparative

Vohra, S.; Reilly, M.; Rac, V. E.; Bhaloo, Z.; Zayack, D.; Wimmer, J.; Vincer, M.; Ferrelli, K.; Kiss, A.; Soll, R.; Dunn, M.	2013	Study protocol for multicentre randomized controlled trial of HeLP (Heat Loss Prevention) in the delivery room	Exclude	inappropriate intervention
Decima, P.; Stephan-Blanchard, E.; Degrugilliers, L.; Delanaud, S.; Leke, A.; Tourneux, P.; Ghyselen, L.; Kongolo, G.; Ramadan-Ghostine, G.; Moreau, F.; Goudgil, S.; Fontaine, C.; Moussa, Y.; Bissuel, M.; Deguines, C.; Bach, V.; Libert, J. P.	2012	Do pre-term neonates sleep better in incubators controlled with air or skin temperature?	Exclude	inappropriate intervention
Deguines, C.; Decima, P.; Pelletier, A.; Degrugilliers, L.; Ghyselen, L.; Tourneux, P.	2012	Variations in incubator temperature and humidity management: A survey of current practice	Exclude	inappropriate intervention
Kaczmarek, J.; Tarawneh, A.; Martins, B.; Sant' Anna, G. M.	2012	Fluctuations in relative humidity provided to extremely low-birthweight infants (R1)	Exclude	non-comparative
Kohler, T.; Augdal, T. A.; Erikson, A.; Hansen, G. A.; Husby, E. M.; Jakobsen, L. M. D.; Lura, B.; Mueller, L. S. O.	2012	Evaluation of dose and image quality of neonatal chest Xrays when using an incubator detector tray	Exclude	inappropriate intervention
Marik,P. E.; Fuller, C.; Levitov, A.; Moll, E.	2012	Neonatal incubators: a toxic sound environment for the preterm infant?	Exclude	inappropriate intervention
Oh, W.	2012	Fluid and electrolyte management of very low birth weight infants	Exclude	inappropriate intervention
Qiu, X.; Lodha, A.; Shah, P. S.; Sankaran, K.; Seshia, M. M. K.; Yee, W.; Jefferies, A.; Lee, S. K.	2012	Neonatal Outcomes of Small for Gestational Age Preterm Infants in Canada	Exclude	inappropriate intervention
Thies, R.	2012	Neonatal portable chest X-rays using the giraffe omnibed X-ray tray and computed radiography: Maintaining diagnostic image quality without increased dose	Exclude	inappropriate intervention
Todorovic, N.; Jovanovic, B.; Jovanovic, N.; Nikolic, M.; Stanojlovic, O.; Ciric Ljubinkovic, V.; Durutovic, J.; Miladenovic Mihailovic, A.	2012	Late preterm babies/LPB/morbidity and mortality	Exclude	inappropriate intervention

Wilson, K.; Nagy, A.; Green, C.; Boyd, D.; Ratnavel, N.; Mohinuddin, S.	2012	Factors influencing early neonatal mortality in retrieved extreme preterm neonates	Exclude	inappropriate intervention
Bell, E. F.; Acarregui M. J.	2011	Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants (review)	Exclude	inappropriate intervention
Chawla, S.; Amaram, A.; Gopal, S. P.; Natarajan, G.	2011	Safety and efficacy of Trans-warmer mattress for preterm neonates: results of a randomized controlled trial	Exclude	inappropriate intervention
Knobel, R. B.; Guenther, B. D.; Rice, H. E.	2011	Thermoregulation and Thermography in Neonatal Physiology and Disease	Exclude	inappropriate intervention
Loersch, F.; Schindler, M.; Starr, K.; Moore, J.; Lynam Bayne, L.	2011	Risk factors for intra-hospital transport of newborn patients: A new solution to an old problem	Exclude	inappropriate intervention
Mouskou, S.; Antonogeorgos, G.; Varakis, C.; Bakoula, C.; Kyritsi, E.; Siahanidou, T.	2011	Factors which are associated with complications during neonatal transport	Exclude	inappropriate intervention
Wubben, S. M.; Brueggeman, P. M.; Stevens, D. C.; Helseth, C. C.; Blaschke, K.	2011	The sound of operation and the acoustic attenuation of the Ohmeda Medical Giraffe OmniBedTM	Exclude	inappropriate intervention
Billock, N.; Dryfhout, V.; Brady, K.; Falciglia, H.	2010	A comparison of mortality and morbidity in multiple versus singleton very low birth weight infants	Exclude	inappropriate intervention
Kim, S. M.; Lee, E. Y.; Chen, J.; Ringer, S. A.	2010	Improved care and growth outcomes by using hybrid humidified incubators in very preterm infants	Include	
Kong,Y. S.; Singh, S.; Tiong, Y. L.; Woo, D.; Cheung, F.; Cheong, J. L. Y.; Courtot, J. E.; Jolley, D.; Martin, C.; Kotsanas, D.; Medhurst, A. M.	2010	A randomised controlled trial to compare the effect of 80% and 70% incubator humidity on the body temperature of infants born at 28 weeks gestation or less: Secondary outcomes	Exclude	inappropriate intervention
McCall, E. M.; Alderdice, F. A.; Halliday, H. L.; Jenkins, J. G.; Vohra, S.	2010	Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants	Exclude	inappropriate intervention
Methlouthi, J.; Zakhama, R.; Nouri, S.; Adouani, M.; Barbouch, H.; Hachi, M. M.; Marzouk, A.; Mahdhaoui, N.; Kairi, H.; Sboui, H.	2010	Morbidity and survival of preterm infants less than 32 weeks gestational age in a NICU level III in Tunisia	Exclude	inappropriate intervention

Moran, M. O. ; O'Donovan, D.	2010	Transfer of preterm infants to open cot at 1800g - A pilot study	Exclude	inappropriate intervention
Sinclair, L.; Crisp, J.; Sinn, J.	2009	Variability in incubator humidity practices in the management of preterm infants	Exclude	inappropriate intervention
Laptook, A. R.; Watkinson, M.	2008	Temperature management in the delivery room	Exclude	inappropriate intervention
AlFaleh K.	2008	Temperatures of extreme low birth weight infants at a tertiary center neonatal unit: A descriptive, retrospective study	Exclude	inappropriate intervention
Chang, A. S. M.; Berry, A.; Sivasangari, S.	2008	Specialty teams for neonatal transport to neonatal intensive care units for prevention of morbidity and mortality	Exclude	inappropriate intervention
Chawla, D.; Agarwal, R.; Deorari, A. K.; Paul, V. K.	2008	Fluid and electrolyte management in term and preterm neonates	Exclude	inappropriate intervention
Higdon, H. L. 3rd; Blackhurst, D. W.; Boone, W. R.	2008	Incubator management in an assisted reproductive technology laboratory	Exclude	inappropriate intervention
Lyon, A.	2008	Temperature control in the neonate	Exclude	inappropriate intervention
McCall, E. M.; Alderdice, F. A.; Halliday, H. L.; Jenkins, J. G.; Vohra, S.	2008	Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants	Exclude	inappropriate intervention
P. H. P. Gray, S.; Finch, G.; Hayes, M.	2008	Computer-generated versus nurse-determined strategy for incubator humidity and time to regain birthweight	Exclude	inappropriate intervention
Wada, M.; Kusuda, S.; Takahashi, N.; Nishida, H.	2008	Fluid and electrolyte balance in extremely preterm infants <24 weeks of gestation in the first week of life	Exclude	inappropriate intervention
Williams, A. L.; Sanderson, M.; Lai, D.; Selwyn, B. J.; Lasky, R. E.	2008	Intensive care noise and mean arterial blood pressure in extremely low-birth-weight neonates	Exclude	inappropriate intervention
Laroia, N.; Phelps, D. L.; Roy, J.	2007	Double wall versus single wall incubator for reducing heat loss in very low birth weight infants in incubators	Exclude	inappropriate intervention
Loersch, F.; Schindler, M.; Dahlmann, S.; Berlet, I.; Lynman, L.; Schaible, T.	2007	From traditional incubator to developmentally-oriented care by using a hybrid (OmniBed)	Include	

Meyer, M. P.; Bold, G. T.	2007	Admission temperatures following radiant warmer or incubator transport for preterm infants <28 weeks: A randomised study	Exclude	inappropriate intervention
Kennell, J. H.	2006	Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200 g to 2199 g newborns	Exclude	inappropriate intervention
Sherman, T. I.; Greenspan, J. S.; St Clair, N.; Touch, S. M.; Shaffer, T. H.	2006	Optimizing the neonatal thermal environment	Exclude	inappropriate intervention
Watkinson, M.	2006	Temperature control of premature infants in the delivery room	Exclude	inappropriate intervention
Knobel, R. B.; Wimmer, J. E., Jr. ; Holbert, D.	2005	Heat loss prevention for preterm infants in the delivery room	Exclude	inappropriate intervention
Gray, P. H.; Paterson, S.; Finch, G.; Hayes, M.	2004	Cot-nursing using a heated, water-filled mattress and incubator care: A randomized clinical trial	Exclude	inappropriate intervention
New, K.; Flenady, V.; Davies, M. W.	2004	Transfer of preterm infants from incubator to open cot at lower versus higher body weight	Exclude	inappropriate intervention
Tunell, R.	2004	Prevention of neonatal cold injury in preterm infants	Exclude	inappropriate intervention
Flenady, V. J.; Woodgate, P. G.	2003	Radiant warmers versus incubators for regulating body temperature in newborn infants	Exclude	inappropriate intervention

Appendix 5: Example Data Extraction Sheet

	Study Characteristics													Results of Outcomes (Average)								
Study Title	Author	Country	Date of Article (Year of Study)	Study Design	Methods	Publication Information	Aim	Population	Number of Study Participants	Mean ±SD GA (weeks)	Mean ±SD BW (g)	Nature of Intervention	Outcomes	Mean ±SD BT	Mean ±SD Weight Loss (% of BW)	Mean ±SD Total Fluid Intake (ml/kg/day)	Mean ±SD Urine Output (ml/kg/hr)	Mean ±SD Na^+ Levels (mEq/L)	Mean ±SD K^+ Levels (mEq/L)	Mean ±SD Glucose Levels (mEk/L)	Mortality	Additional Comments

Appendix 6: Newcastle-Ottawa Scale Quality Appraisal Tool for Cohort Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Appendix 7: GRADE Summary of Findings Table with Explanations

Question: Giraffe OmniBed compared to various existing interventions for treating ELBW neonates

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Giraffe OmniBed	various existing interventions	Relative (95% CI)	Absolute (95% CI)		
Episodes of hypothermia (follow up: 1 weeks)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	A single study reported "no significant difference between groups for total episodes of hypothermia"				⨁◯◯◯ VERY LOW	CRITICAL
Body temperature difference (follow up: mean 1 weeks; assessed with: Celsius)												
2	observational studies	serious [b]	not serious [c]	serious [d]	not serious	publication bias strongly suspected [e]	Study 1: mean rectal temperature at admission was 36.71°C for patients in the Giraffe OmniBed and 37.2°C for historical controls. Study 2: mean admission temperature was 35.7 ± 0.9°C for patients in the Giraffe OmniBed and 35.8 ±1.0°C for those in the conventional incubators.				⨁◯◯◯ VERY LOW	IMPORTANT
Weight loss (follow up: mean 1 weeks; assessed with: % of birth weight)												
1	observational studies	not serious	not serious	not serious [f]	serious	none	Single study: a mean (±SE) 8.0 ±0.6% using the Giraffe OmniBed compared with a 10.8 ±0.7% loss of birth weight using a conventional incubator over 7 days.				⨁◯◯◯ VERY LOW	IMPORTANT
Total fluid intake (follow up: mean 1 weeks; assessed with: ml/kg/day)												
1	observational studies	not serious	not serious [g]	not serious [f]	serious	none	Single study: a mean (±SE) 161± 3.5 ml/kg/day using the Giraffe OmniBed compared with 180.6 ± 4.9 ml/kg/day using a conventional incubator over 7 days.				⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Giraffe OmniBed	various existing interventions	Relative (95% CI)	Absolute (95% CI)		
Urine output (follow up: mean 1 weeks; assessed with: ml/kg/hr)												
1	observational studies	not serious	not serious	not serious [f]	serious	none	Single study: a mean (±SE) 3.7± 0.2 ml/kg/h using the Giraffe OmniBed compared with 4.2 ± 0.2 ml/kg/h using a conventional incubator over 7 days.				⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Only Kim 2010 reported on episodes of hypothermia. The only details they gave were no significant differences in episodes of hypothermia between groups. Very little information on this outcome across studies introduces serious bias.
b. All of the studies were observational. There is a risk of bias in patient selection.
c. Temperatures were taken from different body parts in different studies
d. Outcome was assessed at different time points across studies
e. The abstract remained an unpublished study.
f. Kim et al. were direct in their comparison.
g. Although only one study reported on this it was of high quality