Introduction

The purpose of this document is to draw attention to common objections directed towards Bio-identical hormone replacement therapy. The arguments are summarised under 5 categories;

1. **Issues with the definition of Bio-identicals and management of treatment**
2. **Ethical Issues surrounding BHRT**
3. **Regulatory concerns**
4. **Issues with compounding**
5. **Lack of substantial data through extensive clinical trial**

Each argument is set out with the most common concerns and typical objections referenced. Next, the response to each section is detailed with objection and clarification. This document is intended to draw attention to the criticism of BHRT. At Marion Gluck Clinic we fully welcome the transparent and scientific discussion of Bio-identicals.

The second document is titled “The case for Bio-Identical Hormones’, it is a comprehensive guide to the science of Bio-identicals. The rationale of this second document is to demonstrate the scientific evidence for BHRT and to equip doctors with the most recent findings and studies.

Having read and understood both sections, each doctor will be exposed to common misconceptions concerning BHRT and in turn, be capable of addressing any future questions.

Addressing BHRT concerns

1. **Issues with the definition of Bio-identicals and management of treatment**

   A major concern is the term 'bio-identical' becoming incorrectly synonymous with 'natural' or 'non-synthetic' and should be revaluated to correct patient misconceptions[1]. A more accurate definition of 'bio-identical hormones' is that they have the same molecular structure as the endogenous hormones present in the human body.

   Patients are usually prescribed BHRT based on the hormone levels in their saliva and in some cases blood. These tests have been criticized for showing no correlation between the hormone levels and symptoms thereby being unreliable[2,3]. It is for these reasons that dosing of regulated and licensed hormone preparations is based on providing symptom relief. When salivary tests are used as a basis to influence asymptomatic women into taking hormones they do not need and symptomatic women into taking higher doses that could pose greater risks, this results in clinical ethical problems.

1. Fugh-Berman A, Bythrow J. Bio-identical hormones for menopausal hormone therapy: variation on a theme. *J Gen Intern Med* 2007; **22**: 1030–1034.
2. Boothby LA, Doering PL, Kipersztok S. Bio-identical hormone therapy: a review. *Menopause* 2004; **11**: 356–367
3. The Endocrine Society. *Position Statement: Bio-identical Hormones* 2006.

1. Response

The term "Bio-Identical" was conceptually derived from the bio-mimicking and molecular identity of naturally derived hormones. The primary argument for the case of these naturally derived hormones is based on the molecular structure being identical to those found in Humans, unlike those used in conventional Hormone Replacement Therapy.

The critique of using blood profiles to diagnose and manage menopausal treatment needs to be understood in light of clinical practice. The question of how conventional HRT is recommended and diagnosed is a prudent one that requires elaboration. At MGC we implement and recommend using blood profiles to formulate a snapshot of a patients hormone levels in time. Furthermore, the uses of TSH and FSH blood levels have scientifically established values in the use of them. It is critical to state that blood profiles of patients are

taken as pointers alongside their symptoms and often accompany Ultrasound and Bone density scan. The objectives are to determine if a patient is cyclic or not and then establish the best time to record this 'Snapshot'. At MGC we do not prescribe based on levels of Hormones identified from saliva, instead we build a patients profile by taking extensive medical history combined with blood tests over time intervals to achieve a degree of reproducibility

2. Ethical Issues surrounding BHRT

One of the concerns of the clinical community is the misrepresentation of BHRT where patients perceive this form of therapy to be more effective due to the "natural" label attached to it. According to a statement made in NICE Guidelines; **"compounded bio-identical hormones** are "Unregulated plant-derived hormonal combinations similar or identical to human hormones that are compounded by pharmacies to the specification of the prescriber". Nice further express that for the diagnosis and management of menopause; "the efficacy and safety of unregulated compounded bio-identical hormones are unknown"

Accurate representation of BHRT to the patient needs to be addressed in terms of the benefits and risks as well as the standard of care which fall under the "*ethical principles of respect for persons and beneficence*"[1]. Most patients self educate when seeking out information regarding hormone therapy. Popular press and media coverage, websites run by private practice healthcare professionals can directly impact the patients making informed decisions. It is therefore critical that presentation of BHRT in popular mediums be carried out ethically [2,3,4].

1. Rosenthal, MS. Ethical problems with bio-identical hormone therapy. *International Journal of Impotence Research* (2008) 20, 45–52.
2. Anton B, Nelson R. Literacy, consumer informatics, and health care outcomes: interrelations and implications. *Stud Health Technol Inform* 2006; **122**: 49–53.
3. Reed M, Anderson C. Evaluation of patient information Internet web sites about menopause and hormone replacement therapy. *Maturitas* 2002; **43**: 135–154.
4. Sillence E, Briggs P, Harris PR, Fishwick L. How do patients evaluate and make use of online health information? *Soc Sci Med* 2007; **64**: 1853–1862.

2. Response

MGC promotes the accurate representation and true nature of Bio-identicals, and fully endorse the science of compounding. The clinic aims to empower patients through the unique programme of personalised medicine coupled with comprehensive care. This involves the constant monitoring of symptoms and following up on patients. All patients are subject to Quality of Life questionnaires, bone density scans and Pelvic Ultrasound, all of which are essential to MGC's standard of care.

The criticism by NICE suggesting that the evidence and benefit of BHRT as unknown is addressed in the second document, where comprehensive scientific evidence is provided.

The democratisation of medicine is increasingly changing the dynamics between health care providers and patients. While MGC does not endorse sensational and aggressive marketing overplaying the benefits of BHRT, the clinic believes in empowering patients in making informed decisions. Consultations are long and detailed to ensure patients fully understand the treatment options and are informed about safety of the types of hormones to be prescribed.

Often BHRT is a last resort therapy for patients who have adverse reactions to conventional HRT or who are worried about the safety of it. It is essential to fully probe patient symptoms to work with them to identify the true impact of their hormonal imbalance. This wholesome approach to patient symptoms coupled with prescribing minimum required dosages, are an effective and proven approach to BHRT.

3. **Regulatory concerns**

   Pharmacies compounding bio-identical hormones are not required to track and document adverse effects therefore claiming these hormones are safe due to lack of reports do not equate to nonexistence of risk[1]. Some reports have shown an association of bio-identical compounded hormone therapy with endometrial cancer. This is possibly as a result of insufficient progesterone in non-hysterectomized women receiving estrogen in bio-identical compounded hormone products[2].

   It is also worth mentioning that compounded bio-identical hormones are not required to undergo monitoring for purity or dose standardization by regulatory bodies. They also do not require to carry package inserts and therefore do not contain any potential warning or contra indications[3,4]. Absorption and bioavailability of these compounded hormones are unknown.

Although many compounding pharmacies aim to provide high quality products, there is still threat of undesirable events happening some of which have been well documented. Contamination by various pathogens has been proven as a risk and exemplified by the meningitis outbreak that occurred due to contaminated injections. This was from a single compounding pharmacy[5]. Legal control and regulatory situations of custom compounding vary greatly from country to country and thus are exploited.

1. Davis R, Batur P, Thacker HL. Risks and effectiveness of compounded bio-identical hormone therapy: a case series. *J Womens Health (Larchmt).* 2014;**23**:642-648
2. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with "bio-identical" hormone replacement therapy. Med J Aust. 2007;187:244-245.
3. AACE. American Association of Clinical Endocrinologists (AACE) Reproductive Medicine Committee Position Statement on Bio-identical Hormones. Available at: https://www.aace.com/files/positionstatements/aacebhstatement071507.pdf Accessed March 28, 2017
4. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Compounded bio-identical menopausal hormone therapy. *Committee Opin* 2012; 1–5
5. Smith RM, Schaefer MK, Kainer MA, et al. Fungal infections associated with contaminated methylprednisolone injections. *N Engl J Med* 2013;369:1598–609

3. Response

In light of proper practice, we encourage the regular tracking of patient profiles, and have invested heavily in software to automate exploration of clinical data alongside laboratory results. With a dedicated team to query the scientific rationale behind different treatments, in order to ensure that hormonal levels can be balanced with close monitoring of bone density levels combined with reduction of endometrial hyperplasia. The balancing of hormone levels is linked to regular screening and management of symptoms via automated quality of life questionnaires.

As opposed to diverting the question of side effects by suggesting HRT has well documented and arguably more severe effect on patients, it is critical to highlight the importance of training and constant development of good practice. BHRT is often a last resort for many patients, who have undergone conventional HRT with many stories of bad practice to tell. MGC works closely alongside the specialist pharmacy to constantly develop the 'over and beyond' strategy for BHRT. As a result of this, all medication is subject to rigorous dose standardization while safety information and inserts are provided with every dispensation.

The outbreak of meningitis was due to an invasive procedure that MGC does not indorse or practice. The constant and personal management of doses, with support from peer group and more experienced prescribers at hand to ensure the best possible care. The ability to request tailor made doses for each patient with different delivery options at hand empowers doctors to really micromanage symptoms and patient needs, avoiding the limitation of having to choose from a predefined dosage.

MGC does not promote the '*alternative medicine'* approach to BHRT, although it is clear that hormonal imbalance is related to psychological or cosmetic disorders, at MGC Bio-identicals are used only to manage symptoms and restore the balance of hormones. Often as a result of therapy a plethora of improvements are seen in a patient's quality of life, these are noted and tracked.

4. **Issues with compounding**

   In addition to there being a lack of well-designed clinical studies determining the efficacy of Bio-identical hormones, there is also hardly any research examining safety. Theoretically, bio-identical compounded hormones and commercially available hormones estradiol and progesterone carry the same risk since both are prepared from pharmaceutical-grade products[1]. However, true risk in comparison to commercially available products is not known.

   Doses of compounded hormone products are mostly empiric and those administered exogenously do not correlate with endogenous hormone levels. They are usually affected by factors such as dietary intake prior to testing and the time of day[5]. Hormonal levels are not a reliable indicator of therapeutic response to hormone therapy. The goal is the subjective improvement of menopausal symptoms rather than titration to an unnecessary hormonal level [1-2].

   Last year (2016), the Endocrine society released a statement in the form of a comprehensive review of compounded bio-identical hormones in practice. It suggested that approved, registered, bio-identical hormonal drugs that have been produced in regulated facilities are available and the switch to custom compounded hormones is needless and in some cases harmful. It advised that use of available registered products takes precedence[3].

4. Response

The inherent lack of regulation in the US and Europe has allowed for in some cases bad practice and poor compounding to take hold. For this reason MGC suggests that only suppliers with adequate validation and quality control measures are sourced from, where measures are taken to prevent contamination and are only licenced by GpHC (The General Pharmaceutical Council). Active steps taken by the Specialist Pharmacy to go over and beyond the required regulatory standards in the compounding of Bio-identicals has meant till date, no yellow cards have been flagged for the compounded medications. Prescribing based on hormonal levels alone is agreeably problematic, for this reason, a patients profile must be closely managed and coupled with symptom based and diagnostic information such as ultrasounds and bone density scans.

The safety of BHRT is fully discussed in the document 'the case for bioidentical hormones' with detailed referencing. MGC does not promote the use of given hormonal values to be used as reference points but instead, used as diagnostic tools to ensure the patients symptoms and quality of life also move in the desired direction.

1. Davis R, Batur P, Thacker HL. Risks and effectiveness of compounded bio- identical hormone therapy: a case series. *J Womens Health (Larchmt).* 2014;**23**:642-648

2. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with "bio-identical" hormone replacement therapy. Med J Aust. 2007;187:244- 245.

3. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Compounded bio-identical menopausal hormone therapy. *Committee Opin* 2012; 1–5

5. Lack of substantial data through extensive clinical trial

To date, no large, long-term study has been carried out to determine the adverse effects of bio-identical hormones, so safety concerns remain a serious issue. In addition to this there is a lack of peer reviewed evidence to prove that compounded BHRT formulations are more effective or safer than conventional hormones that are approved by regulatory bodies[1,2,3,4]. A recent systematic review and meta-analysis of bio-identical hormones showed that it did not have significant beneficial effect on menopausal symptoms in women. It also revealed that heterogeneity of the studies available limit the possibility for definitive conclusions[5].

When the WHI (Women's Health Initiative) trial results were published, women were warned against using conventional hormone therapies. Regulatory bodies advised that other formulations should be considered to be of similar risk in the absence of sufficient data[1]. The phrasing "bio-identical" was a tactical way to promote alleged

differences between the hormones used in the WHI trial (conjugated equine estrogen and progestin) from BHRT formulations. The latter were promoted to be much safer than the former FDA regulated preparations even though there was no evidence to substantiate such a claim[6,7]

1. Boothby LA, Doering PL and Kipersztok S. Bio-identical hormone therapy: a review. *Menopause* 2004; **11**: 356–367.
2. Fugh-Berman A and Bythrow J. Bio-identical hormones for menopausal hormone therapy: variation on a theme. *J Gen Intern Med* 2007; **22**: 1030–1034
3. The Endocrine Society. *Position Statement: Bio-identical Hormones* 2006
4. National Institutes of Health. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. *Ann Intern Med* 2005
5. Whedon JM, KizhakkeVeettil A, Rugo Nancy A, and Kieffer Kelly A. Bio-identical Estrogen for Menopausal Depressive Symptoms: A Systematic Review and Meta-Analysis. *Journal of Women's Health*. 2017; 26(1): 18-28.
6. Cirigliano M. Bio-identical hormone therapy: a review of the evidence. *J Women's Health* 2007; **16**: 600–631
7. Naughton MJ, Jones AS, Shumaker SA. When practices, promises, profits, and policies outpace hard evidence: the post-menopausal hormone debate. *J Soc Issues* 2005; **61**: 159–179
8. Harvard Health publications : http://www.health.harvard.edu/womens-health/fda-approved-bio-identical-hormones-for-menopausal-symptoms
9. https://clinicaltrials.gov/ct2/show/NCT01942668

5. Response

The need to balance patient hormones requires a wholesome approach where combinations of hormones are prescribed to achieve the desired effect. A more realistic reason underlying the lack of research in this field is the absence of investigator expertise in endocrinology with sufficient medical training that have been exposed to BHRT. However, this may have changed over the past decade. Few BHRT investigators and prescribers have in fact carried out approved research, they are not considered reliable criticism by peers is often how data presented only serves to reveal risks similar to conventional HRT. This is now beginning to change; four active clinical trials have been initiated for estradioal and progesterone with varying doses and delivery mechanisms. Results demonstrate the first bio-identical combination hormone therapy of estradiol and progesterone to demonstrate safety and efficacy data in a large, well controlled, randomized clinical trial [9].

An inherent limitation of demanding clinical trials from compounded bio-identicals is within the science of personalised compounding. Since compounding hormones is designed to meet each patients required dosage as per the request of the prescriber to reproduce this in a clinical trial is impractical and would fail to meet minimum requirements of reproducibility. How many different doses / ratios of compounded hormones will be required is another

mystery especially where double blinded and placebo settings are taken into account. Finally, it is important to note that there are already approved and regulated “bio-identical” hormones available in the forms of Estrogens, Progesterone and combined hormones, all of which have ‘substantial data into efficacy and safety’ [8].