

A systematic review of non-invasive manual therapies in the management of irritable bowel syndrome

By

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Dissertation submitted in partial compliance with the requirements for the Master's Degree in Technology: Chiropractic

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I, Nannick Badenhorst, do declare that this dissertation is representative of my own work in both conception and execution.

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DEDICATION

I dedicate this dissertation to my late father, Nicolaas J. Badenhorst, my mother, Francina J. Badenhorst, and my son, Jonathan J. Badenhorst.

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.

ABSTRACT

Background:

Practitioners are increasingly required to practice within an evidence-based setting, with the demand being driven by patients as well as health management organisations. This is compounded by large volumes of literature that is available, making it difficult for the practitioner to synthesise and apply this knowledge. A systematic review provides an avenue for literature to be organized, critiqued and available in a condensed form for practitioners. The objective of this study was, therefore, to formulate such a review in order to provide practitioners with consolidated evidence of the efficacy of non-invasive manual interventions for patients with irritable bowel syndrome.

Method:

A systematic search of the literature as well as a hand search were conducted with the following key terms: "irritable bowel syndrome", "conservative", "manual", "manipulation", "manual manipulation", "osteopathic manipulation", "manual therapy", "movement therapies", "physical therapies", "massage", "exercise", "kinesiology", "reflexology", "thermotherapy" and "yoga" (alone and in combination). The databases included: CINAHL Plus, Google Scholar, MEDLINE, Metalib, Pubmed, Science Direct, Springerlink and Summons. Once screened for inclusion and exclusion criteria, a final 18 articles earned inclusion status. The criteria included: **Citation Inclusion-** to be available in electronic format for purposes of accessing the citation; the title to include one or more of the following term(s): irritable bowel syndrome, conservative, manual, manipulation, manual manipulation, osteopathic manipulation, manual therapy, movement therapies, physical therapies, massage, exercise, kinesiology, reflexology, thermotherapy and yoga (alone and in combination). **Full abstract / publication inclusion criteria** -studies published in, or translated to, English; randomised controlled clinical trials, clinical trials, case reports or series and observational studies were included in the study; studies pertaining to the non-invasive manual therapy of IBS (as per the key terms above); studies pertaining to medicinal and non-surgical interventions. **Exclusion criteria** - non-English studies; studies inaccessible in full article format;

studies defined as a systematic review, review of literature or expert opinions. The articles were then individually rated by seven independent reviewers. Ratings were achieved via the application of published and validated scales. These include the Newcastle-Ottawa, PEDRO as well as Liddle rating scales, each specifically formulated to systematically evaluate the methodological rigour of articles as per their particular study type.

Data Collection and Analysis:

The data obtained from the independent reviewers was then analysed and used to rank the articles, first individually according to the results achieved via aforementioned rating scales, and then collectively per intervention to determine the level of evidence in support of the non-invasive manual therapy interventions for irritable bowel syndrome.

Results:

A total of 1542 potential citations were initially identified, with 15 articles enduring the screening process. A secondary hand-search added three additional articles, rendering a total of 18 articles for review. On analysis of the results, it was found that osteopathic care, yoga therapy and traditional Chinese spinal orthopedic manipulation interventions had the strongest and most consistent outcome for positive benefit for IBS patients. Chiropractic care and massage therapy presented with limited evidence, while no evidence was produced in support of reflexology in the treatment of patients with IBS.

Conclusion:

It is evident that future research is required in all of the above fields in order to expand on the limited available evidence while addressing the limitations of previous studies, as highlighted in this systematic review. This would strengthen the literature and allow for improved clinical decision making based on available evidence that is of high quality and practical value.

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DEFINITIONS:

Borborygmi: “rumbling noises caused by the propulsion of gases through the intestines.” – Dorland’s Medical Dictionary

“Floor” and “Ceiling” Effects:

These phenomena come into play when elements of a study design (e.g. sample size or outcome measures) lack in their capacity to assess the full range of physical function of a population, i.e. are unable to measure the extremes. For example, a *floor* effect is when *all* the participants score near the bottom, with either an inadequate sample size and/or demographic representation of the study population, or outcome measures that do not produce variance in data (e.g. questionnaires that are too difficult or do not include assessment of extreme cases viz. the severely affected). Conversely, a *ceiling* effect viz. when all the participants score near the top (again without significant variance in data), either the outcome measures do not adequately assess those participants with no functional impairment (the extreme opposite to severely affected participants), or the questionnaires are too easy. In the case of inadequate demographic representation or size of the sample population, when there are not enough items to capture, the full range of participant functional ability cannot be adequately described, and therefore may hamper the ability of the researcher to extrapolate the study’s findings to the general population (Bruce *et al.* 2013)

Hawthorne Effect: “any form of artifact or consequence of research participation on the behavior of the participant...awareness of being observed or assessed engenders beliefs about researcher expectation, conformity and social desirability considerations then lead behavior to change in line with these expectations.” – McCambridge *et al.* (2013)

Hypochondriasis: “a mental disorder characterized by the preoccupation with bodily functions and the interpretation of normal sensations (such as heart beats, sweating and bowel movements) or minor abnormalities (such as a runny nose, minor aches and

pains, or slightly swollen lymph nodes) as indications of highly disturbing problems needing medical attention. Negative results of diagnostic evaluations and assurance by physicians only increase the patient's anxious concern about his/her health, seeking further medical attention." – Dorland's Medical Dictionary (1994)

Incidence: "the rate at which a certain event occurs, e.g., the number of new cases of a specific disease occurring during a certain period." – Dorland's Medical Dictionary (1994)

Incidence Rate: "a fraction expressing the rate of new cases of a disease in a population over a period of time: the numerator is the number of new cases during a specified time period, and the denominator is the population at risk during this time." – Dorland's Medical Dictionary (1994)

Intervention: "The act undertaken aimed to treat or cure a condition." (Haldeman 2005)

Manual Therapy: Manual for the purpose of this study, refers to any therapy (including motion therapy) or manipulations (including chiropractic, osteopathic, spinal and orthopedic manipulations, applied kinesiology, acupressure, massage) of body tissues, muscle and bones by hand or equipment to improve health and circulation, relieve fatigue and/or promote healing. – PubMed MeSH terms (2016)

Non-invasive Therapy: Any therapy that is applied to the soma (anything derived from the ectoderm of the embryo) from an external force, which does not involve the introduction of instruments, fluids or chemicals to the body. – PubMed MeSH terms, 2016)

Placebo: "any dummy treatment administered to the control group in a controlled clinical trial in order that the specific and non-specific effects of the experimental treatment can be distinguished – i.e. the experimental treatment must produce better

results than the placebo in order to be considered effective.” – Dorland’s Medical Dictionary (1994)

Placebo Effect: “the sum total of all non-specific effects, both good and adverse, of medical treatment, primarily psychological and psycho-physiological effects associated with the physician-patient relationship and the patient’s expectations and apprehensions concerning the treatment.” – Dorland’s Medical Dictionary (1994)

Prevalence: “the number of cases of a disease that are present in a population at one point in time.” – Dorland’s Medical Dictionary (1994)

Prevalence Rate: “the percentage of a population that present with a disease at a given time: the numerator is the number of existing cases of a disease at a point in time, the denominator is the total population.” – Dorland’s Medical Dictionary (1994)

Sample: “a small part or amount considered to be representative of the larger body or community.” – Mouton (1996)

Somatisation: “in psychiatry, the conversion of mental experiences or states into bodily symptoms.” – Dorland’s Medical Dictionary

Somatoform: “physical symptoms in the absence of medical disorder” – North *et al.* (2007)

Spinal manipulation: A physical procedure which is performed on the spine of the patient by chiropractors, osteopaths and physical therapists – Haldeman (2005)

Systematic Review: “a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research.” – Cochrane Library (2011); “and present all the evidence on a specific subject” –Liberati *et al.* (2009)

ABBREVIATIONS:

CBT:	Cognitive Behavioural Therapy
CRP:	C-Reactive Protein
CS:	Case study / series (case report)
ESR:	Erythrocyte Sedimentation Rate
F:	Female
FAP:	Functional Abdominal Pain
FBC:	Full Blood Count
FBDSI:	Functional Bowel Disorder Severity Index
FGID:	Functional Gastrointestinal Disease
FSS:	Functional Somatic Syndrome
HAD:	Hospital Anxiety and Depression
IBS:	Irritable Bowel Syndrome
GSRS:	Gastrointestinal Symptom Rating Scale
M:	Male
MERGE:	Methods for Evaluating Research and Guideline Evidence
NOS:	Newcastle Ottawa Scale
n-RCT:	Non-randomised clinical trial
n-RCTs:	Non-randomised clinical trials
OMT:	Osteopathic Manipulative Therapy
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD:	Post-traumatic Stress Disorder
RCT:	Randomised clinical trial
RCTs:	Randomised clinical trials
SMT:	Spinal Manipulative Therapy
SR:	Systematic Review
TCSOM:	Traditional Chinese Spinal Orthopedic Manipulation
VAS:	Visual Analogue Scale
WBC:	White Blood Count
WGO:	World Gastroenterology Organisation

CHAPTER ONE

INTRODUCTION

1.1 Introduction

Irritable bowel syndrome (IBS) is the most common diagnosis in gastroenterologists' practices, accounting for 28% of all their patients (Lovell and Ford 2012a). According to the American Gastroenterological Association, IBS affects 14% to 24% of women and 5% to 19% of men in the United States, most European countries, China and Japan (Drossman *et al.* 2002). The prevalence of IBS in South Africa was found to be similar to that of western countries (Walker and Segal 1993).

In context, IBS is classified as a functional gastrointestinal disorder (FGID), comprising a group of common, chronic gastrointestinal (GI) conditions that manifest in the absence of pathological abnormalities (Fichna and Storr 2012; North *et al.* 2007).

IBS usually presents as a cluster of gastrointestinal symptoms that relapse episodically, posing challenges to both the patient as well as the practitioner in their approach to managing this disorder. The cardinal symptoms include abdominal pain or discomfort, bloating and altered bowel habits (Croghan and Heitkemper 2005). These symptoms have a significant negative impact on daily life, with a resultant inferior quality of life in IBS sufferers (Jones *et al.* 2006). This is associated with reduced productivity in the workplace (Dean *et al.* 2005, DiBonaventura *et al.* 2011), which ultimately has a negative economic impact on the patient and society at large (Peery *et al.* 2012). In the U.S. alone, the economic impact is estimated at \$ 25 billion annually through direct health costs and indirect costs of absenteeism from work (Longstreth *et al.* 2006).

Successful treatment options are therefore important, not only for symptomatic relief, increased sense of wellbeing of the patient and reduced impact on the sufferers' immediate community , but could also reduce complications including diverticulosis,

ulceration of the bowel, malabsorption syndromes and other associated conditions e.g. gallstones, kidney stones and arthritis (Loomis 2001).

Effective therapies are currently limited for this functional gastrointestinal disorder (Whitfield and Shulman 2009). Due to the chronic nature of this condition, patients are required to seek long term palliative treatment, more conventionally comprised of chronic medication. A report by the United States Food and Drug Administration (U.S. F.D.A.) compiled on patients' perspectives of symptoms and medical treatments related to IBS, revealed that most reported taking or having taken drug therapies to help reduce their symptoms. The drugs were described as having varying degrees of effectiveness. Many participants either switched medications or sought out other therapeutic modalities, due to their intolerance to medication side effects (U.S. Food and Drug Administration 2016).

Other therapeutic modalities sought may be broadly categorised into dietary modification, psychotherapies, electrotherapies, miscellaneous interventions (e.g. herbal, Chinese medicine, movement therapy) as well as manual therapies (Brandt *et al.* 2009). These various categories include a combination of both invasive and non-invasive techniques (Hussain and Quigley 2006). Of these, patients were found to prefer non-invasive techniques as they are often more tolerable (U.S. Food and Drug Administration 2016). Very little is known about the role that these non-invasive techniques play in the management of IBS, particularly the manual therapies. Along with the development and progression of manual health care professions, there have been a number of clinical trials (randomised and non-randomised) and case studies that have been performed to investigate and document the effectiveness of various non-invasive, manual treatment modalities in the management of IBS related symptoms (Spanier *et al.* 2003); so to reduce the financial (U.S. Food and Drug Administration 2016; Weinberg *et al.* 2014) as well as physical (Dekel and Fass 2003) burden of the pharmaceutical interventions. This in turn may improve the overall management of the disorder as well as the patients' well-being (Vlieger 2008).

This research project therefore aimed to serve as a summation of available scientific evidence regarding non-invasive, manual treatment modalities available in the management of IBS. This may offer patients and practitioners valuable insight into effective alternative measures available to manage this chronic disorder, while developing a platform for future research (Juni *et al.* 2001; Moher *et al.* 2007).

A thorough literature review by the researcher provided a final 18 publications on the topic of IBS and available for quality assessment. Several of these studies have, however, been fragmented (Wagner 1995; Amalu 1998) seemingly underfunded (Munton 1999; Brands *et al.* 2011) and as a result poorly organised. This may hamper the availability of information on these modalities to practitioners and / or patients (Grundmann and Yoon 2014). However, Moons and Grobbee (2002) point out that one manner in which the current evidence for non-invasive modalities could be analysed and presented to improve their application is a systematic review. Being a thorough and efficient research method, a systematic review, aims at identifying, selecting and critically assessing previously conducted research, by performing an in depth analysis of the data obtained from the included studies. (Moher *et al.* 2015; Buchbinder *et al.* 2006; Cook, Sackett and Spitzer 1995).

1.2 Rationale

In compiling a systematic review, strict guidelines have to be followed to firstly identify the relevant studies; following which the critical assessment of these studies, and lastly to produce a summation of the evidence that was found on the related topic. When these guidelines for composing a systematic review are stringently followed, medical professionals are be provided with unbiased summaries of the evidence available regarding specific topics (Silva *et al.* 2014).

Due to the constant influx of new information in the medical field, systematic reviews have grown more popular and become greatly beneficial to all medical professions (Crombie and Davies, 2009) as it allows practitioners to devise the most effective

treatment protocols based on the collective results of various individual studies (Higgins and Green 2011; Crombie and Davies 2009; Bullock 2001) without having to endure the often lengthy research process themselves.

This research project therefore aimed to serve as a summation of available scientific evidence regarding non-invasive, manual treatment modalities available in the management of IBS. This may offer patients and practitioners valuable insight into effective alternative measures available to manage this chronic disorder, for which successful conventional treatment is currently limited.

1.3 Aim and Objectives

The *aim* of this study was to determine the level of evidence available to support the use of non-invasive therapies in the management of IBS. The *objectives* were:

1. To identify all studies which have investigated the effectiveness of non-invasive therapies in the management of IBS via electronic data base searches.
2. To perform a secondary hand search of studies that may have not been found via electronic searches.
3. To determine the rigour of the various studies conducted on non-invasive manual therapies in patients with IBS by applying the following quality assessment scales: PEDro Scale (Appendix E) to RCTs, Newcastle-Ottawa Scale (Appendix G) to nRCTs and Liddle Scale (Appendix I) to case studies and case reports.
4. To determine which non-invasive manual therapies have been employed by patients with IBS.
5. To support or refute the level of evidence to support the use of non-invasive manual therapies in patients with IBS.
6. To summarise the level of evidence for each modality and correlate this with clinical outcomes achieved in the respective studies.
7. To make recommendations with regards to future investigations concerning non-invasive manual therapies in patients with IBS.

1.4 Acknowledged Limitations of this Systematic Review

Being an academic exercise, this research project was limited by budget constraints as well as time-frame restrictions within the context of the Master's Degree arrangement.

The following limitations were therefore imposed on this systematic review:

- Articles that were not published in, or translated to, the English language were not eligible for inclusion into this systematic review, which meant that a small number of publications could not be reviewed, as time and budget constraints did not allow for translation of non-English studies. This is considered a form of publication bias.
- The reviewers who participated in this study, were equipped with the individual rating scales, as well as guidelines as to the methods of applying these scales to ensure consistency in scale application. Training was not going to be viable in this instance, and although reviewers were able to seek clarity regarding the scales from the researcher, both the scales as well as their application guidelines were open to individual interpretation. This could mean that inconsistency may have set in among the individual rating of the studies on the review. In an attempt to reduce this interpretation bias, candidates with previous experience in systematic reviews were approached to participate.
- As a means of expanding literature coverage, so to provide a comprehensive summation of available evidence (Mahood, Van Eerd and Irvin 2013; Higgins and Green 2011), "grey literature" (viz. Munton 1999 – Dissertation, DUT Steve Biko Library) was not excluded from this systematic review. This form of literature may, however, introduce certain biases to a systematic review. These will be discussed under Section 2.4.4.1 of this study.

1.5 Chapters' Contents

This chapter provided an introduction to the research topic with regards to its problem and context within the field of manual therapies. The aim and objectives were highlighted along with the rationale for the study. The following chapters will provide further understanding of the research problem arising from the literature review (Chapter Two) and methodology employed in this study (Chapter Three). An analysis of the results obtained from this systematic review will be provided in Chapter Four, with a detailed discussion per therapeutic modality in Chapter Five and in conclusion, a summary of the findings and recommendations in Chapter Six.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

This chapter will review the literature on irritable bowel syndrome (IBS). It will describe IBS in the context of its epidemiology, postulated pathophysiology, clinical features, diagnosis, current management protocols, as well as the patients' perspectives of these prescribed regimes. Following which, the literature pertaining to the history and professional development of manual therapies, as well as patients' inclination toward alternative therapeutic modalities for more effective relief of their IBS-related symptoms will be reviewed. In conclusion, the rationale for conducting a systematic review of non-invasive manual therapies in the management of IBS is contextualised by describing the contribution it could make toward the development of evidence-based healthcare.

2.2 Irritable Bowel Syndrome

IBS is described as a functional gastrointestinal disease (FGID) which manifests in the absence of “anatomical, structural or biochemical abnormalities” in the affected part of the gastrointestinal tract (Fichna and Storr 2012; Chang and Talley 2010; North *et al.* 2007; Longstreth *et al.* 2006). This disorder is characterized by chronic or periodically relapsing abdominal pain or discomfort associated with bloating and disturbed bowel habits ranging from constipation to diarrhoea (El -Salhy 2015; Rey and Talley 2009; Drossman *et al.* 2002). These recurring symptoms severely impact on many facets of a person's quality of life including their diet, sleep, sexual function, travel and socializing (Usher *et al.* 2013; Amouretti *et al.* 2006; Faresjo *et al.* 2006). The five categories of this condition include IBS-D (diarrhoea predominant), IBS-C (constipation predominant), IBS-M (mixed with alternating bouts of diarrhoea and constipation), PI-IBS (post-infective) and US-IBS (unsubtyped IBS) (Quigley *et al.* 2009; Thebane and Marshall 2009; Spiller and Garsed 2009).

2.2.1 Epidemiology

IBS is the most commonly observed disorder in gastroenterologists' practices, accounting for 28% of all their diagnoses (Lovell and Ford 2012a), and depending on the diagnostic criteria employed and other sociological factors, it affects 5-30% of the global population (Liu and Hou 2011).

2.2.1.1 Global Prevalence and Incidence

According to a review by the World Gastroenterology Organisation (WGO) (Quigley *et al.* 2015), current statistics available on the global prevalence and incidence rates of IBS lack in accuracy as well as completion, with several regions worldwide not having produced any relevant data to include in an epidemiological context. This is particularly true in regard to statistics available for the African continent. While this dearth in data may create the impression that IBS is rare among African nations, statistics provided by prevalence studies in Nigeria prove to the contrary (Adeniyi *et al.* 2017; Okeke *et al.* 2009). Reporting prevalence rates ranging between 16.1 and 33%, the findings of these studies may not be adequate to extrapolate across all other African nations, however, they do adequately highlight the importance for further studies across the continent. Another factor that impedes a researcher's ability to effectively and reliably compare data from different geographical regions is that various health-care systems use different diagnostic criteria, for example, less rigid criteria may result in higher reported prevalence rates and vice versa. However, what is noteworthy about the available data (Quigley *et al.* 2015; Canavan *et al.* 2014), is that the prevalence of IBS is rather similar worldwide, notwithstanding significant differences in cultural lifestyles and socio-geographical circumstances.

Despite the grey areas of reporting IBS to the WGO, Quigley *et al.* (2015) summarised its prevalence worldwide, which succeeded a similar publication by Canavan *et al.* in 2014.

Table 2.1 presents the combined data from these two reports, ranging from lowest to highest rates [arranged top to bottom; left to right (reference is made to the respective set of data from which the particular prevalence rate was extracted)].

Table 2.1: Global IBS Prevalence Rates

France: 1.1-4.7% *	China: 0.8-11.5%* -Beijing: 0.82%** -Southern China: 5.7%** -Hong Kong: 6.6%** -Out-patient population:15.9%**	Brazil: 17%*
Thailand: 5.7%*	Germany: 12.5%*	New Zealand: 3.3-18.8%*
Netherlands: 5.8%*	Australia: 4.4-13%*	Russia: 19%*
Italy: 7.2%*	Pakistan: 14%*	Columbia: 19.9%*
Iran: 7.1%*	Canada: 13.5%*	USA: 3-20.4%* : 10-15%**
South Africa: 8.1%*	Japan: 6.1-14%*	Taiwan: 22.1%**
Norway: 8.4%*	Spain: 3.3-14.1%*	UK: 6.1-21.65%*
Bangladesh: 8.5%*	Romania: 14.4%*	Greece: 21.4%*
Turkey: 6.3-10.2%*	Sweden: 12.5-15%*	Peru: 15.0-24%*
Uruguay: 10.9%**	South Korea: 6.6-15.5%*	Croatia: 28.2%*
Singapore: 2.3-11%*	Malaysia: 15.6%*	Iceland: 17.2-30.9%*
Israel: 2.9-11.4%*	Finland: 5.1-16.4%*	Nigeria: 27-36%* -Students: 26.1%** -Outpatients: 33%**
	Venezuela: 16.8%**	

Key: *Canavan *et al.* 2014

**Quigley *et al.* 2015

Meta-analyses reveal an assembled estimate of global IBS prevalence of 11.2% (Lovell and Ford 2012a; Canavan *et al.* 2014). The variations between different countries' data could be ascribed to the use of different diagnostic criteria (Mearin *et al.* 2001; Saito *et al.* 2000) as well as differences in access to, and quality of, health care worldwide (Quigley *et al.* 2015). Other factors that may contribute to the variance in reported rates, include cultural differences (e.g. dietary practices) as well as specific societal and/or environmental stressors (e.g. war/ civil conflict and political/societal oppression). While the impact of stress on IBS as well as the co-morbidity with other psychological disorders (viz. anxiety, depression, posttraumatic stress disorder (PTSD), somatoform disorders) is described in Section 2.2.2 of this dissertation, it is important to consider when reflecting on global prevalence rates, especially for countries with histories of civil conflict (Levy and Sidel 2009). Pedersen (2004) reports the short and long term effects of war on a population's health. Anxiety, depression as well as post-traumatic stress disorder (PTSD) become highly prevalent, with women and children disproportionately affected (Ghobarah, Huth and Russett 2003). Children who grow up in a conflict region suffer from intergenerational effects of mental disease, as well as an ongoing stress burden, for example, a child who inherits an impaired chemical (cortisol) stress response through parental trauma, will have difficulty coping with subsequent stressful situations that face them in later life. Such early trauma may affect them post-traumatically even if they no longer lived in conflict scenarios (Devakumar *et al.* 2014). In another study, Paul *et al.* (2013) describes that Indian parents put excessive pressure on their children to achieve and the associated stress may be a probable cause for the recent increased prevalence of IBS amongst Indian children.

The prevalence of IBS in primary care (i.e. the proportion of sufferers who seek healthcare for their symptoms) ranges from 10 – 70% (Hungin *et al.* 2003; Koloski *et al.* 2003). American studies consistently report that 30% of sufferers will consult a healthcare provider, of those 80% have diarrhoea-predominant IBS (Drossman *et al.* 1993; Hungin *et al.* 2003).

Few studies describe the *incidence* of IBS. Due to the insidious nature of symptoms that often does not require medical care, discrepancies exist between when the disease first manifested, and when it was first diagnosed (Hungin *et al.* 2003). A study conducted in the USA reported an incidence rate of 67 per 1000 person-years (Talley *et al.* 1992). Studies that used a doctor's first diagnosis reported a more conservative rate of two per 1000 person-years (Agreus *et al.* 1995; Garcia Rodriguez *et al.* 2000; Locke *et al.* 2004).

2.2.1.2 Demographic observations of IBS patients

a) Gender:

According to the American Gastroenterological Association (AGA), IBS affects 14-24% of women and 5-19% of men in the USA, most European countries, China and Japan (Lovell and Ford 2012b; AGA 2002). Globally, overall rates among females are 1.5 to three-fold higher than those seen among males (Heitkemper and Jarrett 2008; Andrews *et al.* 2005; Cremonini and Talley 2005; Berman *et al.* 2000; Drossman *et al.* 1999). However, according to Lovell and Ford (2012b), these results are in contrast to studies undertaken in South Asia, South America and Africa, as these authors' reports state that IBS affect males and females similarly. In fact, higher prevalence rates are reported in Indian men than Indian women, which may reflect the gender differences in health care access in some communities (Merzel 2000). A number of studies have been conducted to investigate possible factors why females are more likely to be diagnosed with IBS. Unruh (1996) cites cultural background as women in Western countries are more likely to seek medical care than men. Blanchard *et al.* (2001) as well as Lydiard (2001) concluded that women are more sensitive to psychological distress and life event stress. Mulak *et al.* (2014), Heitkemper and Chang (2009) as well as Ruigomez *et al.* (2003) describe the female sex hormones as contributing factors, as these are known to affect visceral hypersensitivity and lower the individual's pain threshold. Possible gender-related differences in how the central nervous system synthesizes the neurotransmitter

serotonin, may account for visceral perception and illness behaviour (Nishizawa *et al.* 1997).

b) Age: IBS has been diagnosed in people of all age groups with the estimated prevalence among children being comparable to that among adults (Canavan *et al.* 2013). The disorder reportedly occurs mainly between ages 15 to 65 years (Quigley *et al.* 2015). Fifty percent of sufferers first report their symptoms before age 35 (Maxwell *et al.* 1997), whereas only 25% of sufferers report their symptoms over the age of 50 (Lovell and Ford 2012a). This finding may suggest that symptoms abate over time, which interestingly opposes the idea that IBS is a lifelong condition in which the prevalence should increase with age or at least remain constant.

c) Socioeconomic status: Drossman *et al.* (1999) suggest that IBS is associated with people who have a lower income status. This result reinforces the hypothesis that lower income is associated with increased life stresses, lower overall quality of life as well as inferior health care support (Marmot *et al.* 2012). However, other studies suggest the contrary, in that people who earn a high salary are more likely to be diagnosed with IBS which contributes to a higher prevalence of IBS under this socioeconomic category (Mendall and Kumar 1998). This may be as a result of higher and more internalised stress levels perceived by those in managerial and professional positions (Grodzinsky *et al.* 2012). This finding substantiates the notion that IBS is a disease of urbanization and/or industrial development which may explain the increase in prevalence rates observed in Asia, South America and Africa in recent years (Gwee 2012). The rise in financial prosperity among these populations may be associated with a change of diet (Hulshof *et al.* 2003) as well as better access to superior quality health care which may result in more effective identification of IBS (Cremonini and Talley 2005). It may also be considered that the higher prevalence rates observed among these developing nations be a consequence of raised levels of education, which may drive them to seek medical treatment for IBS related

symptoms. In another study, Howell *et al.* (2004) investigated the influence of childhood socioeconomic environment and concluded that childhood affluence was an independent risk factor for the development of IBS.

d) Genetic factors: The risk of developing IBS is twice as high in persons who have a biological relative who suffer from this disorder (Locke *et al.* 2000). Familial studies suggest that having a parent with IBS is an independent risk factor for having IBS, and even stronger a marker than a twin having IBS (Levy *et al.* 2009). This suggestion highlights that adopted behaviour attributes to the heredity of IBS more so than genetic factors, (Saito *et al.* 2010).

2.2.1.3 Economic impact of IBS on patients and society

IBS-related symptoms have a significant negative impact on the daily lives of sufferers (WHO 2015). Apart from enduring the clinical symptoms, patients also require greater consumption of medical which can become economically burdensome (Nellesen *et al.* 2013). Studies have reflected a poorer quality of life in these patients (Jones, Wessinger *et al.* 2006) associated with loss of working hours, reduced productivity in the workplace (DiBonaventura *et al.* 2011, Dean *et al.* 2005; Hungin *et al.* 2005) having a negative economic impact on the patient and society at large (Peery *et al.* 2012). In the US alone, the economic impact is estimated at \$25 billion annually through direct health care costs, and indirect costs of absenteeism from work (Longstreth *et al.* 2006).

Studies reveal that IBS sufferers miss, on average, twice as many work or school days than individuals without the disorder (Talley 2008; Dean *et al.* 2005). Indirect medical costs are incurred through absenteeism as well as presenteeism (i.e. reduced levels of productivity at work (Cash *et al.* 2005). According to Talley (2008), IBS related symptoms account for 3.65 million physician consultations per annum, incurring IBS patients direct costs of up to \$10 billion, not including the cost of any medications, prescribed or over-the-counter (Talley 2008). Van Tilburg *et al.* (2008) found that in the US alone, the annual expenditure per IBS patient to be: \$1084 on pharmacy costs, \$628 on low-GI costs, \$325 on over-the-counter medication, with a total health expenditure of on average \$6059.

2.2.2 Pathophysiology and aetiological factors

The pathophysiology of IBS remains largely misunderstood, as no organic cause can be identified (North *et al.* 2007). The disease does not fit the conventional biomedical model (Phillips *et al.* 2014), by which a single cause is identified and targeted by the appropriate medication for example a bacterial infection which is resolved by the administration of antibiotic medication. Evidence suggests that multiple factors play a pivotal role in the pathophysiology, contributing to the manifestation of the array of IBS related symptoms (El-Salhy 2015). This complex, multi-factorial disorder is therefore best depicted by the *bio-psychosocial* model (Phillips *et al.* 2013; Tanaka *et al.* 2011; Drossman *et al.* 1999 – Appendix L) which describes IBS related symptoms as a combined effect of the sufferer's *biology* (genetic and gastrointestinal physiology), *psychological* susceptibility (personality traits, psychological distress, coping capacity, behavioural trends and higher cognitive function) and the sufferer's *social* environment (life experiences, stress, trauma, social learning and reinforcement) (Phillips *et al.* 2013; Tanaka *et al.* 2011).

The lack of any definite approach to the management of IBS may be due to the lack of understanding, its underlying pathophysiology as well as the interaction of dietary, lifestyle and psychological factors (Snelling 2006).

The emphasis of recent studies has shifted from a “unidirectional” interface between psychosocial aspects (e.g. trauma and stress) and gastrointestinal function, to a “reciprocal” interface of psychosocial and physiologic processes in functional gastrointestinal diseases (FGIDs) (Tanaka 2011; Drossman *et al.* 1999).

2.2.2.1 Brain-gut interactions

Healthy patterns of bowel movements rely on optimal communication between the CNS, enteric nervous system (ENS) and the hypothalamic-pituitary-adrenal (HPA) axis, a system referred to as the *brain-gut axis* (Phillips *et al.* 2014; Phillips *et al.* 2013; Fichna and Storr 2012; Koloski *et al.* 2012; Tanaka *et al.* 2011; Collins and Bercik 2009). Communication along this axis occurs through neural, hormonal as well as immunological pathways (Tanaka *et al.* 2011). It is widely postulated that FGIDs result

from disordered brain-gut interactions (Phillips *et al.* 2014; Fichna and Storr 2012; Jones, Dille et al. 2006; Drossman *et al.* 1999) leading to the dysregulation of brain-gut neuroenteric systems (Xing *et al.* 2013; Fichna and Storr 2012).

This dysregulation is theorized to result in *visceral hypersensitivity* as well as abnormal *gut motility*, two factors believed to contribute to the manifestation of IBS related symptoms (Farrugia *et al.* 2014; Fichna and Storr 2012; Yin and Chen 2010; Eriksson *et al.* 2008; Drossman *et al.* 1999). These factors are as follows:

- a. *Visceral hypersensitivity*: IBS sufferers have a heightened sensitivity to gut stimuli and intensified responsiveness to somatic and visceral symptoms (Barbara *et al.* 2011; Zhou *et al.* 2011; Berman *et al.* 2008). This may result in an overreaction to normal physiological actions that take place during the digestive process e.g. gut contractions and/or abdominal stretching that occurs during peristalsis and/or flatus formation. In other words, IBS patients tend to perceive pain or discomfort from eating sensations that are not perceived at all by those people without the disorder (Fichna and Storr 2012; Eriksson *et al.* 2008; Xiao and Liu 2004; Mayer 2013).
- b. *Abnormal gut motility*: Intestinal muscles contract and relax in a coordinated fashion to produce a rhythmical peristaltic movement in order to pass food from the mouth through the GI tract, and waste to the rectum at an optimal speed. This to ensure optimal rates of absorption and stool passage. In IBS sufferers, the regulation of these events are found to be altered (Yin and Chen 2010; Manabe *et al.* 2009) in so far as intestinal contractions may be more intense, resulting in more rapid passage of food and waste which may manifest as diarrhoea (Florance *et al.* 2012; Kuttner *et al.* 2006). The opposite effect may also arise, with weaker than normal intestinal contractions retarding the rate of peristalsis, resulting in the formation of hard, dry stools which may manifest as constipation and abdominal distension (Love *et al.* 2014; Yu and Rao 2014).

2.2.2.2 Genetic factors

Familial clustering of IBS has been reported with more than a third of sufferers describing a family history of the disorder (El-Salhy 2015; Kanazawa *et al.* 2004). A study conducted in the US found a noteworthy association between IBS sufferers and having an immediate family member with the disorder (Locke *et al.* 2004). This finding was supported by Waehrens *et al.* (2015) who conducted a nationwide survey in Sweden. Prevalence rates for families with IBS are reported to be 21-50% (Saito *et al.* 2010).

According to a number of researchers, *twin studies* confirm the genetic element in IBS (Makker *et al.* 2015; Ford *et al.* 2014; Lembo *et al.* 2007; Bengtson *et al.* 2006; Levy *et al.* 2001). These have shown that the occurrence rate for IBS among monozygotic (identical) twins is two to three times more than among dizygotic (non-identical) twins (Ford *et al.* 2014; Lembo *et al.* 2007; Bengtson *et al.* 2006; Levy *et al.* 2001). One study conducted in Britain, however, reported no significant differences in rates of IBS between dizygotic and monozygotic twins (Mohammed *et al.* 2005).

The aforementioned evidence suggests the potential involvement of specific genes in the pathogenesis of IBS, with most of the *genetic research* focusing on genes effective in the serotonin signalling pathways, intestinal secretions, neuropeptide activity, bile acid synthesis and control of immune activation (El-Salhy 2015). These studies have, however, not produced strong enough evidence to validate any one genotype as a true predisposing factor for IBS (Henstrom and D'Amato 2016; Makker *et al.* 2015; D'Amato 2013).

It may be considered then, that familial clustering of IBS could rather be a consequence of *parental reinforcement* and *adopted behaviour*, substantiated by findings that having a mother with IBS is as strong a predictor as having an identical twin with the disorder (Levy *et al.* 2001). The occurrence of IBS in spouses has also been noted (Waehrens *et al.* 2015). This further suggests that environmental more so than genetic factors are accountable for familial clustering of the disorder (Surdea-Blaga *et al.* 2012). However, a more recent study by Waehrens *et al.* (2017) concluded that IBS was transmitted to

adoptees from their biological parents to a higher degree than from their adoptive parents. This result implies that genetic factors do in fact play an important role in the familial aggregation of IBS.

2.2.2.3 Dietary factors

IBS sufferers largely believe that specific foods may trigger their symptoms (Simren *et al.* 2001). According to Ostgaard *et al.* (2012), the triggers that usually set off sensitivities include dairy and wheat products, eggs, cabbage, onions, legumes, fried and smoked foods, hot spices and caffeine. To investigate what foods some people may be sensitive towards, a number of researchers undertook various immunological studies to identify and define food sensitivities (Hussain and Quigley 2006). Zar *et al.* (2005) found (in their population of IBS patients) elevated levels of IgG antibodies to gluten/wheat, egg, milk, pork, lamb and beef and once these patients excluded these foods from their diet, their symptoms significantly improved. This result was reproduced in a study conducted by Atkinson *et al.* (2004). Lee and Park (2014) state that the mechanism by which these foods may contribute to IBS symptoms has been attributed to inadequately absorbed carbohydrates. These carbohydrates viz. “fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) include fructose, lactose, sources of glucose, fructans and galactans” (Dimidi *et al.* 2017; Gibson *et al.* 2017; Varju *et al.* 2017; El-Salhy 2012). This is because they provide a substrate for bacterial fermentation in the distal small intestine as well as the colon, and this leads to the formation of gas with resultant abdominal distension, which causes abdominal pain or discomfort (Muir 2013; Ostgaard *et al.* 2012). An Israeli study showed that 82% of IBS patients presented with lactose malabsorption, with 70% fructose-sorbitol malabsorption, and 43% fructose malabsorption (Goldstein, Braverman and Stankiewicz 2000). Compliance to a low-FODMAPs diet has shown to reduce symptoms and improve the quality of life (Gibson *et al.* 2017; Varju *et al.* 2017; Halmos *et al.* 2014; De Giorgio *et al.* 2015; Ong *et al.* 2010). The role that FODMAPs play in IBS could, however, be more complicated than mere excessive gas production (Lowe and Moseley 2014). More recent studies have shown that FODMAP may negatively influence the GI

endocrine cells as well as the intestinal microbiota (Mazzawi *et al.* 2015), both of which have been described as contributing factors to healthy gut functioning

. 2.2.2.4 *Gastrointestinal endocrine cells*

Intestinal stem cells give rise to endocrine cells that hormonally regulate several gastrointestinal functions e.g. motility, absorption, local immune response, appetite and satiety, working with the CNS and ENS to ensure optimal GI functioning (El-Salhy 2015). Various studies have shown that there is a reduction in density of these intestinal endocrine cells in people suffering from IBS (El-Salhy *et al.* 2014). This reduction is attributed to a decline in the intestinal stem cell proliferation and differentiation, which in turn, is regulated by specific signalling pathways. It is postulated that genetic and dietary factors along with the integrity of the intestinal microbiota may interfere with the signals that regulate stem cell actions (El-Salhy 2015). This can result in IBS related symptoms viz. visceral hypersensitivity, intestinal dysmotility as well as abnormal gut secretions. Endocrine cells secrete hormones to regulate appetite and satiety, these include ghrelin, cholecystokinin, peptide YY, enteroglucagon and serotonin (El-Salhy *et al.* 2014). While ghrelin stimulates appetite and weight gain, the others have an anorexogenic (to cause reduction in appetite) function (El-Salhy 2015). Research has shown that the density of endocrine cells that secrete ghrelin is increased in IBS sufferers, while the densities of cells that secrete the hormones with an anorexogenic function are reduced (El Sahly *et al.* 2014). This may explain why an association, albeit a controversial one, has been established between IBS and obesity in some sufferers (Pickett-Blakely 2014).

2.2.2.5 *Intestinal microbiota*

Intestinal microbiota (a.k.a. the human microbiome) refers to the more than 1000 bacterial species that colonise the human intestine (Major and Spiller 2014; Ohman and Simren 2013). Some species play an important role in gastrointestinal motility, food digestion and metabolism, gut immune defence, inflammation and cell proliferation (Farrugia *et al.* 2014), while others are responsible for infection and/or inflammation (Tana *et al.* 2010). It is important that a balance between these beneficial and harmful

species be maintained for optimal gut function and absence of disease, as the greater the bacterial biodiversity, the healthier the gut (Carroll *et al.* 2012). The GI bacterial composition is influenced by genetic as well as environmental factors which include method of delivery at birth, exposure to antibiotics, sanitation levels and the aging process (Power *et al.* 2014). Disruption of the intestinal microbiota, aka “dysbiosis” (Chassard *et al.* 2012), is postulated to contribute to the pathogenesis of IBS (Major and Spiller 2014, Parkes *et al.* 2008). Studies have confirmed that diminished levels of lactobacilli and bifidobacteria (both beneficial species) are observed in IBS patients. This is most marked in diarrhoea predominant IBS (IBS-D), causing this subtype patient to hold a particularly lower bacterial biodiversity (Carroll *et al.* 2012), which often leaves them in a state of microbial imbalance. Another observation in IBS patients is increased ratios of anaerobic species (e.g. streptococci and *Escherichia coli*) (Maukonen *et al.* 2006). The positive results achieved in treating IBS symptoms with prebiotic, probiotic and strain-specific antibiotic medication promotes the contribution of altered gut microbiota to the pathogenesis of IBS (Yoon *et al.* 2014; Hoveyda *et al.* 2009; McFarland and Dublin 2008).

2.2.2.6 Low-grade inflammation

Studies suggest that a low-grade inflammation occurs in patients with post infectious IBS (PI-IBS), a subtype which represents 7-31% of IBS sufferers (Spiller and Campbell 2006). Elevated levels of mast cells and immune cells have been identified on a rectal biopsy (Gwee *et al.* 2003). It can, therefore, be postulated that a low-grade inflammation could contribute to the pathogenesis of one subtype of IBS.

2.2.2.7 Stress, history of violence and abuse; and other psychological factors

A bio-psychosocial model (Appendix J) of disease is applied to explain the interface between GI, emotional and cognitive functions, where a dysfunction of brain-gut interactions is depicted to result in FGIDs (Phillips *et al.* 2014; Tanaka *et al.* 2011; Jones, Dille *et al.* 2006). In this model, it is shown that stressful life events as well as psychological factors exacerbate IBS symptoms, influence health care seeking behaviour (Levy *et al.* 2006) as well as impact on clinical outcomes i.e. improved

symptom intensity (Tanaka *et al.* 2011). Psychological distress and trauma are widely reported by patients with FGIDs, with significant associations between IBS and depression (Ford, Brandt *et al.* 2009; Jones, Dille *et al.* 2006; Lackner *et al.* 2004), anxiety (Myers and Greenwood-Van Meerveld 2009; North *et al.* 2007; Spence and Moss-Morris 2007) and PTSD (Savas *et al.* 2009; Dobie *et al.* 2004).

Stress is associated with the pathogenesis of IBS as well as the exacerbation of related symptoms (Phillips *et al.* 2014; Blanchard *et al.* 2009; Blanchard and Scharff 2002). This relationship has been demonstrated through administering corticotrophin-releasing hormone (CRH) to patients and confirming improvement in their CRH-receptor antagonists (Dinan *et al.* 2006; Sagami *et al.* 2004). IBS sufferers tend to process stressful situations differently to individuals without the disorder, which may influence somatic and visceral symptoms (Kennedy *et al.* 2014; Rey *et al.* 2009). The human body continually adapts to stress to regain stability and maintain homeostasis (Phillips *et al.* 2014). This process is known as allostasis and describes optimal functioning as a product of continual modifications of physiological systems as the body adapts to environmental stresses (Phillips *et al.* 2014). Continual stresses can, however, be harmful to the brain and body which may result in a state of allostatic “load” that can manifest physically and predispose individuals to certain disorders, one of which is IBS (Lackner *et al.* 2004).

A history of *sexual* and *physical abuse* and exposure to *violence* is widely reported by sufferers of FGIDs (40-53%) (Leserman and Drossman 2007; Drossman *et al.* 2003; Drossman, Creed *et al.* 1999; Talley *et al.* 1998). However, this finding is mirrored in patients with other chronic pain conditions (Lampe *et al.* 2003) and therefore cannot be considered pathognomonic for FGIDs. It may, however, predispose the individual to developing physical symptoms in response to psychological stress (Drossman *et al.* 2003). In a study to investigate the prevalence and association of IBS with psychological distress among American female war veterans, Savas *et al.* (2009) determined high prevalence rates of IBS, at 38% it was relatively higher than that reported among women in the general population of Western countries viz. 5-27% (Drossman, Camilleri *et al.* 2002). They also found a significant association between IBS

symptoms and increased presence of depression, anxiety and PTSD among these war veterans. Apart from the stresses of separating from family, and the violence associated with armed conflicts, these female veterans also reported high rates of military sexual assault, with the reported prevalence of rape during military service ranging between 11 and 48% (Goldzweig *et al.* 2006).

Exposure to *violence* has been associated with long-term effects on the health, brain structure and neural function in children (Glaser 2000). These effects may result in mental health conditions, most commonly depression, anxiety, somatoform disorders and PTSD, all of which seem to correlate strongly with IBS (Moscardino *et al.* 2012; Dobie *et al.* 2004).

Psychiatric disorders most frequently observed in IBS sufferers include the following: anxiety disorders (generalized as well as panic anxiety disorders), mood disorders (major depression), somatoform disorders (somatisation and hypochondriasis) as well as PTSD (North *et al.* 2007; Cohen *et al.* 2006; Dobie *et al.* 2004; Mayer *et al.* 2001; Irwin *et al.* 1996). These disorders were observed in 50% to 90% of IBS patients who presented to gastroenterology clinics (North *et al.* 2007), versus 25% in control groups (Drossman, Creed *et al.* 1999).

Although no specific personality profile has been established for IBS, common *personality traits* have been observed in these individuals. Higher levels of anxiety and neuroticism (e.g. Type A personality profile) may predispose the individual to IBS (Farnam *et al.* 2007; Hazlett-Stevens *et al.* 2003; Talley *et al.* 1998; Drossman, Whitehead *et al.* 1997). In conclusion, the different influences of emotions, thought processes and environmental stresses on GI function and health, contribute to the variation of symptoms observed in patients with IBS, explaining how psychosocial trauma or inadequate coping measures can exacerbate symptoms of the disorder (Savas *et al.* 2009; Levy and Sidel 2009; de Jong *et al.* 2003) as well as influence the outcome thereof. It is, therefore, no longer viable to ascertain whether psychological or physiological aspects cause IBS related symptoms, but rather to accept that both these factors are influential in the manifestation of the disorder. The task at hand for health

care providers is to ascertain the level to which each contributes and to which degree these can be remedied (Drossman, Creed *et al.* 1999).

2.2.3 Clinical features

IBS presents as a cluster of chronic gastrointestinal symptoms that relapse episodically (North *et al.* 2007). The cardinal symptoms include abdominal pain or discomfort, abdominal bloating and altered bowel habits ranging from constipation to diarrhoea, sometimes with alternating bouts of constipation and diarrhoea and passing of mucoid stools (Croghan and Heitkemper 2005). The clinical features of IBS can vary widely from person to person, which has led to the sub-classification of the disorder (Spiller *et al.* 2007). The different IBS types (Dorn *et al.* 2009; Quigley *et al.* 2009; Thebane and Marshall 2009; Spiller and Garsed 2009; Ersryd *et al.* 2007) are described according to the individual's stool as defined by the Bristol Stool Scale (Drossman 2006; Longstreth *et al.* 2006).

Table 2.2 Subclassification of IBS (Adapted from WGO, Quigley *et al.* 2015)

<p>IBS with diarrhea (IBS-D):</p> <ul style="list-style-type: none"> - Loose stools more than 25% of the time - Hard stools less than 25% of the time - Accounts for up to a third of cases, more predominantly in males
<p>IBS with constipation (IBS-C):</p> <ul style="list-style-type: none"> - Hard stools more than 25% of the time - Loose stools less than 25% of the time - Accounts for up to a third of cases, more predominantly in women
<p>IBS with mixed habits or cyclic pattern (IBS-M)</p> <ul style="list-style-type: none"> - Both hard and loose stools more than 25% of the time - Accounts for a third to a half of diagnosed cases
<p>Un-subtyped IBS</p> <ul style="list-style-type: none"> - Insufficient abnormality of stool consistency to fall under IBS-C/M
<p>Post-infectious IBS (PI-IBS)</p> <ul style="list-style-type: none"> - Develops as a consequence of an intestinal infection

2.2.4 The impact of clinical features on a person's Quality of Life

It is widely reported that IBS related symptoms have a significant negative impact on people's daily life (FDA 2015; Nellesen *et al.* 2013; Drossman, Morris *et al.* 2009; Jones, Wessinger *et al.* 2006; El-Serag 2003; Motzer *et al.* 2003). A survey conducted by the US Food and Drug Administration (2015) gives valuable insight to the physical, social and emotional impact that IBS as a FGID has on their daily lives.

The following problems were described:

- *Inability to enjoy food* was highlighted as a major impact on their enjoyment of daily living. Participants noted that pain, feeling full after ingesting only a small amount, bouts of diarrhoea directly after ingesting a meal, as well as having to avoid certain food types had a significant impact on their lives as well as restricting their social lives.
- *Difficulty caring for self or family members*: Pain and altered patterns of defecation (ranging from constipation to *diarrhoea*) sometimes limited the sufferer's ability to care for their families and in some reported cases these individuals even had to rely on caregivers to assist them in their daily activities.
- *Restrictive work and / or academic performance*: Symptoms were reported to hamper their ability to optimally perform in the work place or classroom. Some participants reported the inability to attend meetings in the case of an episode of diarrhoea or severe abdominal pain. As discussed in the epidemiology of IBS, sufferers also miss on average twice as many work or school days.
- *Negative emotional and social impact*: Participants described daily frustrations and emotional distress caused by FGIDs symptoms. It is difficult for them to socialize and lead normal lives with their families. For example, they reported that gas and flatulence caused much embarrassment and their families, and hampered their ability to engage socially. Some people reported that they felt ostracised as a result of their symptoms as they were no longer invited to social gatherings.

- *Patients' perspectives on specific IBS related symptoms:*
 - Patients clearly described their abdominal pain and discomfort as separate symptoms; discomfort as a dull, persistent yet tolerable ache, and abdominal pain as debilitating, temporary and often triggered by specific foods and/or drinks.
 - Patients complained of abdominal distension or bloating as a daily occurrence that can be as severe as to hamper the ability to breathe with ease. Some patients even reported that abdominal bloating was so severe that they even had difficulty fitting into uniforms or appropriate safety gear required in the workplace.
 - Some patients reported that flatulence release not only caused much embarrassment, but at times was extremely painful.
 - Constipation and diarrhea are depicted as significant symptoms, each with their own sets of difficulties and restrictions, impacting severely on individual's personal, social as well as working roles and relationships.

2.2.5 IBS Diagnosis

The diagnosis of IBS presents as a challenge to consulting physicians as no physical signs or biochemical abnormalities are detectable, making it very difficult to pinpoint the existence of the disorder (Nellesen *et al.* 2014; Fichna and Storr 2012). There are no specific biomarkers to clearly indicate the reason for a person's complaints (Fichna and Storr 2012), therefore IBS is identified via a clinical process of exclusion (Canavan *et al.* 2014). To standardise and define IBS, and thereby facilitate a more definitive diagnostic approach, experts compiled a set of *diagnostic criteria* based on key presenting symptoms (Drossman 2006). The first was created by Manning and colleagues in 1978 (Manning *et al.* 1978). Manning's criteria enabled doctors to positively diagnose IBS, without the need for extensive and costly laboratory testing employed in the process of exclusion. In the intervening years, however, and through further research, clinicians added more restrictive criteria to that of Manning's diagnoses which resulted in the formulation of the Rome Criteria (Canavan *et al.* 2014; Drossman 2006). Rome I was developed in 1989 (Saito *et al.* 2000, Table 2.3) and succeeded by Rome II in 1999

(Drossman *et al.* 2000; Thompson *et al.* 1999), with the most recent Rome III criteria published in 2006 (Drossman 2006). The diagnostic criteria have evolved somewhat over the past 17 years, and continue to do so with the upcoming Rome IV expected for release in 2016 (Quigley *et al.* 2015).

Table 2.3 IBS diagnostic criteria (Adapted from Canavan *et al.* 2014)

Manning Criteria (1978)	Rome I (1989)
<p>Two or more of the following symptoms:</p> <ul style="list-style-type: none"> • Abdominal distension • Pain relief with defecation • Frequent stools with pain • Looser stools with pain • Passage of mucous • Sensation of incomplete evacuation 	<p>At least three months of continuous or recurrent abdominal pain:</p> <ul style="list-style-type: none"> • Relieved with defecation or • Associated with change in stool consistency • With at least two of the following on at least 25% of days: <ul style="list-style-type: none"> - Altered stool frequency - Altered stool form - Altered stool passage - Passage of mucous - Bloating or distension
Rome II (1999)	Rome III (2006)
<p>At least twelve weeks in the past twelve months of continuous or recurrent abdominal pain or discomfort.</p> <ul style="list-style-type: none"> • With at least two of the following: <ul style="list-style-type: none"> - Relief with defecation - Altered stool frequency - Altered stool form - Onset of symptoms more than twelve months before diagnosis 	<p>At least three days per month in past twelve weeks of continuous or recurrent abdominal pain or discomfort</p> <ul style="list-style-type: none"> • With at least two of the following: <ul style="list-style-type: none"> - Relief with defecation - Altered stool frequency - Altered stool form - Onset of symptoms more than six months before diagnosis

Clinicians, however, often do not adhere to these diagnostic criteria, and instead base their diagnosis on *clinical* findings (e.g. bloating and psychological stress) (Mearin and Lacy 2012).

During a consultation with a prospective IBS patient, the doctor needs to focus on the primary presenting clinical features, as well as identify precipitating factors. This is because IBS symptoms commonly manifest co-morbidly with other GI symptoms for example dyspepsia, gastro-oesophageal reflux disease (GORD) and functional constipation (Lovell and Ford 2012c; Sperber and Dekel 2010). Doctors, therefore, need to enquire of their patient's medical and psychological history to rule out "red flags" - i.e. signs and symptoms of serious disease (Welch 2011) - that would warrant further investigation. These "red flags" include the following of which doctors need to enquire about (Quigley *et al.* 2015; De Giorgio *et al.* 2004):

- Age of symptoms and if new onset of symptoms after age 50.
- Unexplained weight loss.
- Rectal bleeding.
- Fever of unknown origin.
- Nausea or recurrent vomiting.
- Abdominal pain, not relieved by defecation, or occurring at night.
- Persistent diarrhoea that may occur during sleep.
- Iron deficiency anaemia.
- Family history of colorectal cancer, celiac disease and/or inflammatory bowel disease.
- History of recent travel to the tropics/subtropics.

Other points to address during a thorough history taking should include:

- The pattern of abdominal pain or discomfort – duration, type, location, relieving and precipitating factors, previous episodes.
- Other abdominal symptoms- bloating, distension, borborygmi, flatulence.
- Nature of onset (sudden versus e.g. PI-IBS).

- Nature of the associated bowel disturbances – constipation, diarrhoea and alteration.
- Abnormalities of defecation – urgency, mucous, feeling of incomplete evacuation.
- Issues relating to menstruation.
- Current and past drug therapies.
- Diet – consumption of foods known to cause intolerance (milk, gluten, artificial sweeteners, alcohol).
- Family history of IBS.
- Persistent diarrhoea – this should prompt more extensive investigation for other causes.

Furthermore, a detailed *physical examination* is of cardinal importance. Not only to identify possible organic causes of presenting symptoms, but also to reassure the patient of physician competence and vested interest in his/her case. A thorough physical examination should be executed for signs of systemic disease, following which an abdominal examination including the peri-anal as well as rectal regions (Haslett *et al.* 2002).

In patients under the age of 40 years, a clinical diagnosis can be confidently reached without having to resort to extensive or complicated laboratory testing (Quigley *et al.* 2015). Full blood count (FBC), Erythrocyte Sedimentation Rate (ESR) and faecal occult blood tests (FOBT) are routinely performed in these patients, whereas barium enema and/or colonoscopy investigations are reserved for those patients above the age of 50 years to exclude colorectal malignancy (Quigley *et al.* 2015; Boon *et al.* 2002). Further useful *investigations* include stool culture (especially for those individuals whom present with diarrhoea) and the hydrogen breath test for lactose intolerance and bacterial overgrowth (Shen and Yaso 2009).

Psychological assessment may be helpful to identify previously discussed psychological factors that may influence patient perception of abdominal symptoms and contribute to a diminished quality of life (North *et al.* 2007; Drossman, Creed *et al.* 1999) and excessive use of healthcare (Quigley *et al.* 2015).

The following objective assessment measures are recommended to identify any psychological features, as stipulated by the WGO (Quigley *et al.* 2015):

- The Hospital Anxiety and Depression Scale (HADS) measures levels of anxiety and depression (Stern 2014).
- The Sense of Coherence (SOC) test to identify individuals with low SOC whom respond to cognitive behavioural therapy (Eriksson and Lindstrom 2006).
- The Patient Health Questionnaire (PHQ-15) identifies the presence of multiple somatic symptoms (Han *et al.* 2009).

A standardised, global approach to the diagnosis and subsequent management of IBS may often not be viable or practical. This is because the epidemiology, clinical presentation as well as the availability of diagnostic and management resources, are not sufficiently homogenous worldwide to support the existence of a single, gold standard protocol (Quigley *et al.* 2015). The World Gastroenterology Organisation Global Guideline (2015) stipulates the following set of “cascades” to provide *resource-sensitive* (i.e. according to the patient’s economic status) options for the diagnosis of IBS:

Low resource levels

- History, physical examination, exclusion of “red flags”, consideration of psychological factors.
- FBC, ESR, CRP and stool examination.

Medium resource levels

- History, physical examination, exclusion of “red flags”, consideration of psychological factors.
- FBC, ESR, CRP, Stool studies (WBC, ova, parasites, occult blood).
- Sigmoidoscopy (reserved for cases based on patient’s age and clinical features as well as geographical location e.g. areas of high prevalence for inflammatory bowel disease, celiac disease, colon cancer or parasitosis).

High resource levels

- History, physical examination, exclusion of “red flags”, consideration of psychological factors.
- FBC, ESR, CRP, Stool studies (WBC, ova, parasites, occult blood).
- Thyroid function testing.
- Tissue transglutaminase (TTG) antibody testing to screen for celiac disease.
- Esophagogastroduodenoscopy (EGD) and distal duodenal biopsies in patients with diarrhoea, to rule out celiac disease, tropical sprue, giardiasis, and in patients where the abdominal pain and discomfort is predominantly in the upper abdomen.
- Colonoscopy and biopsy (reserved particularly for those patients over the age of 50 or presenting with “red flag” symptoms).
- Faecal inflammation marker to distinguish IBS from inflammatory bowel disease.
- Hydrogen breath test for lactose intolerance and small-intestinal bacterial overgrowth.
- Selenium homocholic acid taurine (tauroselcholic acid) test (SeHCAT; incorporating selenium-75) for bile acid malabsorption and measurement of bile pool loss.

Accurate diagnosis is not only important to ensure appropriate treatment, but will also safeguard the individual from any unnecessary risk and costs involved in further *needless* investigative testing [National Institute for Health and Clinical Excellence (NICE) – Dalrymple and Bullock 2008).

Differential diagnoses to consider when assessing a patient for IBS include the following (Quigley *et al.* 2015):

- Bile acid malabsorption (BAM) – adult onset BAM is considered an important cause of IBS-D related symptoms. A review by Slattery *et al.* (2015) found that more than 25% of IBS-D patients present with BAM.
- Colorectal carcinoma – especially in older patients who develop IBS related symptoms for the first time.

- Microcytic colitis – accounts for more than 20% of unexplained painless diarrhoea.
- Acute or chronic diarrhoea due to protozoan parasites or bacteria – in their review of the involvement of intestinal protozoa in IBS, Stark *et al.* (2007) concluded that there was “a possible role for protozoan parasites, such as *Blastocystis hominis* and *Dientamoeba fragilis*” in the pathogenesis of IBS. The clinical diagnosis of amebiasis is often complicated, as IBS related symptoms may closely mimic those of nondysenteric amebic colitis.
- Small-intestinal bacterial overgrowth (SIBO) – this may be a rare option, unless the patient is immune-compromised, has undergone surgical procedures, or suffers from a primary or secondary motility disorder. Some SIBO symptoms may overlap with those of IBS (e.g. bloating and diarrhoea) and although it has been suggested that SIBO may be related to IBS, it is generally believed not to be a common cause.
- Tropical sprue – in returning travellers with persistent diarrhoea.
- Diverticulitis – in patients with focal lower left-sided abdominal pain. Yamada *et al.* (2014) found that left-side as well as bilateral diverticular disease may increase the risk for IBS.
- Endometriosis – cyclical lower abdominal pain.
- Pelvic inflammatory disease – fever with chronic lower abdominal pain.
- Ovarian cancer – in women over the age of 40.
- Colitis associated with nonsteroidal anti-inflammatories (NSAIDs) –for e.g. in the elderly who receive treatment for arthritic pain.
- Inflammatory Bowel Disease (IBD) – Crohn’s Disease (CD) and Ulcerative Colitis (UC)

Co-morbidity with other diseases is also common, and patients with overlap syndromes tend to suffer more severely of IBS related symptoms (Przekop *et al.* 2013; Lovell and Ford 2012; Sperber and Dekel 2010; Hillila *et al.* 2007). Some clinicians believe that these conditions should be grouped together under the single “umbrella” term of *functional somatic syndromes* (FSS) (Heningsen *et al.* 2007).

These FSS include the following:

- Fibromyalgia manifests in up to 50% of IBS patients (WGO 2015; North *et al.* 2007; Whitehead *et al.* 2002; Sperber *et al.* 1999).
- IBS is common in the following chronic pain syndromes (WGO 2015) :
 - In 51% of patients with chronic fatigue syndrome- known as myalgic encephalomyelitis (Perrin *et al.* 1998).
 - In 64% of patients with temporomandibular joint disorder (North *et al.* 2007).
 - In 50% of patients with chronic pelvic pain syndrome.
- Non-ulcer dyspepsia is reported to correlate with IBS (Henningesen *et al.* 2007).
- Celiac disease – Ford, Chey *et al.* (2009) found the prevalence of biopsy-confirmed celiac disease to be more than four times higher in patients diagnosed with IBS than in ‘control’ group of individuals without IBS.
- Chronic Idiopathic Constipation (CIC) – There is a high prevalence of this condition in IBS patients. Clinicians are faced with a clinical conundrum in distinguishing between the two disorders as the symptoms are so similar. Soares and Ford’s (2009) study questions the viability of the existing “artificial division” between these two FGIDs (Soares and Ford 2009).
- Gastro-esophageal Reflux Disease (GERD) – Lovell and Ford (2012) found the prevalence of GERD to be four times higher in IBS patients than in patients without IBS, because 25% of the symptoms overlap. Therefore, routine screening for gastroesophageal reflux symptoms in IBS patients is recommended.
- More than 50% of IBS patients suffer from depression and/or anxiety (Przekop *et al.* 2013; Tang *et al.* 2012; Hamilton *et al.* 2009). These patients are reported to suffer more severe somatic symptoms (Lackner *et al.* 2013).

2.2.6 Management of IBS

Successful management begins with reaching a positive diagnosis and reassuring patients that their symptoms do not arise from a more sinister organic cause. The cornerstone of IBS management is a strong patient-clinician relationship based on empathy and education. Communication about the risk to benefit ratios of available treatment protocols has been found to increase compliance and positively affect treatment outcome, patients who understand the reason for their prescribed medication are more likely to adhere to the management protocol (Miller *et al.* 2006).

The first line of defence includes dietary and lifestyle modifications, coupled with medication to address presenting symptoms (Quigley *et al.* 2015; Grundmann and Yoon 2014; Li and Li 2015; Shen and Yaso 2009). Due to the chronic nature of the disorder, sufferers are required to seek long term palliative treatment most conventionally comprised of chronic medication.

2.2.6.1 Dietary and lifestyle modification

In many cases, simple modifications in the individual's lifestyle and diet may prove enough to resolve, or at least contain, their IBS symptoms. These modifications include dietary changes (Simren 2014), regular exercise (Lustyk *et al.* 2001), cessation of smoking as well as avoiding alcohol and caffeine (Grundmann and Yoon 2014; Li and Li 2015).

i. Dietary changes:

Diet plays an important role in symptom exacerbation for many people with IBS (Hayes *et al.* 2013), with positive responses to *exclusion diets* ranging from 15% to 71% (Niec, Frankum and Talley 1998). Exclusion diets may benefit patients with proven intolerance to most frequently identified foods, for example: milk, gluten, sugar and eggs. However, there is a paucity of evidence available to clinically say that this is the 'gold standard' to relieving symptoms (Brandt *et al.* 2009; Snelling 2006). According to Spanier *et al.* (2003), removing these recommended foods from one's diet, may risk nutritional deficiencies, and what foods may help

one symptom may exacerbate another, for example: Increasing the amount of *fibre*-rich foods, particularly soluble fibre, have been reported to reduce constipation, although this could lead to flatus and abdominal bloating and/or cramping. Insoluble fibre (e.g. nuts and wholegrains), however, should be avoided as they may exacerbate overall IBS symptoms. According to Shen and Yaso (2009), fibre should be gradually increased over a period of a few weeks while monitoring the effect on symptoms. Patients are also advised to exclude gas-producing foods that could contribute to bloating, abdominal distension and diarrhoea. Diets that restrict the intake of FODMAPs have proven effective in IBS symptoms (Dimidi *et al.* 2017; Varju *et al.* 2017) reporting a positive response rate of around 70% (Gibson 2017).

Shen and Yaso (2009) provided specific guidelines for dietary changes in IBS, as adapted from the National Institute for Health and Clinical Excellence (Dalrymple and Bullock 2008). These are as follows:

- Eat regular meals and do not rush eating.
- Do not skip or leave long gaps between meals.
- Drink at least eight cups of fluid a day, particularly water and non-caffeinated drinks for e.g. herbal teas.
- Avoid drinking more than three cups of tea or coffee a day.
- Reduce intake of alcohol and carbonated drinks.
- In cases of diarrhoea consider limiting the intake of high-fibre foods (e.g. brown rice, whole-wheat breads, cereals high in bran) and avoid the sorbitol (artificial sweetener) found in “sugar-free” sweets, gum, drinks, diabetic as well as slimming products.
- Reduce the intake of resistant starches found in processed foods.
- Avoid eating more than three (80 gram) portions of fresh fruit per day.
- In cases of flatulence and/or bloating, eat oats and linseeds (up to one teaspoon per day).
- Manage fibre intake, only soluble fibre is recommended.

- If trying probiotics, vary the species of bacteria for greatest suitability. Probiotics need to be taken for at least four weeks at the recommended dose, and to preferably record whether it has an effect on symptoms.

ii. **Lifestyle modifications:**

Common lifestyle modifications, apart from implementing the discussed dietary changes, include increased physical activity with regular exercise, abstinence from alcohol, nicotine and caffeine, increased water intake, stress management (Shen and Yaso 2009) as well as forming healthy and regular sleeping patterns (Li, Tahir and Li 2015). Increased physical activity is often recommended as a primary treatment in IBS as various studies have indicated that symptoms decrease (Johannesson *et al.* 2011). Other studies report that physical activity can improve an individual's mood, while reducing stress, fatigue, bloating as well as abdominal discomfort (Grundmann and Yoon 2014; Daley *et al.* 2008) . Lustyk *et al.* (2001) found regular exercise to increase gastrointestinal motility in IBS-C patients, while De Schryver *et al.* (2004) reported improved colonic transit times and defecation patterns in patients with chronic constipation.

2.2.6.2 Medical management

The treatment strategy is aimed at the nature and severity of symptoms, the degree of functional impairment, and the presence of psychosocial factors that may influence the course and outcome of the condition. The Task Force on IBS of the American College of Gastroenterology (ACG) and the British Society of Gastroenterology have developed current guidelines on how to manage IBS (Brandt *et al.* 2009; Jones *et al.* 2000). However, both these associations acknowledge a remarkable placebo effect associated with their palliative treatment (from 20-70%). This has been confirmed by numerous studies (Kaptchuk *et al.* 2010; Conboy *et al.* 2006; DeGiorgio *et al.* 2004) which

supports the notion that a patient's emotions and mood disorders influences the severity of IBS related symptoms (Grundmann and Yoon 2014).

- i. **Antispasmodics (smooth-muscle relaxants)** are commonly used in both IBS-D and IBS-C patients and serve to provide short-term relief of abdominal pain and cramping (Li and Li 2015; Jailwala *et al.* 2000). Coupled with diet and lifestyle modifications, antispasmodics generally comprise the first-line therapy protocol (Quigley *et al.* 2015). However, none of these antispasmodic medications are specific for IBS and caution should be taken in IBS-C patients as they serve to further reduce GI motility. Research has found that there are some antispasmodics that directly relax the smooth intestinal muscle relaxation viz. *mebeverine* and *pinaverium bromide*, and other antispasmodics that act as anticholinergic agents viz. *dicyclomine* and *hyoscyamine* (Ruepert *et al.* 2011; Ford *et al.* 2008). These are commonly associated with a host of cardiovascular side effects ranging from postural hypotension, tachycardia to cardiac arrhythmias (Li and Li 2015; Chang 2014; Grundmann and Yoon 2014; Martinez-Vazquez *et al.* 2012; Ru, Darvish-Damavandi *et al.* 2010; Drossman *et al.* 2002). Other adverse effects associated with antispasmodics include dry mouth, drowsiness and dizziness, exacerbation of constipation, urinary retention, blurred vision, raised intra-ocular pressure (to be considered in IBS patients with glaucoma), confusion, impaired memory and even hallucinations (Fox *et al.* 2014). Ford *et al.* (2014) concluded that adverse effects were more common with antispasmodics than with a placebo. As a result of these adverse effects and the intermittent nature of IBS pain, Freeman (2010) suggested that these medicines only be taken as-needed or in anticipation of known precipitating factors and/or exacerbating stressors.
- ii. **Anti-diarrheal agents** such as *loperamide* (Imodium) are beneficial to IBS-D patients as these opioid agonists serve to slow down gut transit as well as enhance intestinal water and electrolyte absorption (Freeman 2010). This in turn reduces stool frequency and improves stool consistency (Ford *et al.* 2014). It is, however, no more effective than a placebo in relieving pain, bloating and other

global IBS symptoms, and considering the high risk of dependency associated with any opioid-related substances, it is not widely recommended for IBS patients (Hanauer 2007; Brandt *et al.* 2002).

- iii. **Prokinetics** are aimed at enhancing GI motility, and are therefore recommended to IBS-C patients (Ford, Brandt *et al.* 2009). They are described as receptor targeted drugs and act either via dopamine and 5-HT₃ receptors as antagonists (for IBS-D) or 5-HT₄ as agonists (for IBS-C). *Tegaserod* is currently the only FDA approved prokinetic that is specific for the treatment of IBS-C. Strong evidence suggests the effectiveness of this drug, however, the high incidence of increased cardiovascular risk severely limits its use (Ford, Brandt *et al.* 2009; Tack *et al.* 2006; Evans *et al.* 2007; Brandt *et al.* 2002; Jones *et al.* 2002). It has reportedly been removed and re-introduced to the market only for the use in female IBS patients (Freeman 2010). *Lubiprostone* is generally only prescribed for women with severe constipation who have not responded to other treatment. Side effects include nausea, diarrhoea and abdominal pain, and its long-term safety has not been established (Ford *et al.* 2014; Grundmann and Yoon 2014; Johnson 2008; Lang 2008; Lesbros-Pantoflickova *et al.* 2004). Other 5-HT₄ agonists often prescribed include *metoclopramide* and *domperidone*.

Alosetron is the most recommended 5-HT₃ antagonist with strong evidence available to support its efficacy in relieving visceral pain in female IBS-D patients (Cremonini *et al.* 2012; Bleser 2011). While it may cause a host of side effects including gastric upset, bloating, hemorrhoids, ischemic colitis, headaches and depression (FDA 2016), the effect of alosetron on male IBS patients has not yet been established (Fukudo and Matsueda 2014). Investigation into the efficacy of a *novel* 5-HT₃ antagonist viz. *ramosetron hydrochloride*, proved the drug to be effective and well-tolerated for both male and female IBS-D patients (Fukudo and Matsueda 2014; Matsueda *et al.* 2008). Furthermore, ramosetron holds less risk of ischemic colitis, rendering it the safer option for IBS-D patients (Fukudo and Matsueda 2014).

- iv. **Peptide agonists** act to increase intestinal fluid secretion, thereby accelerating GI transit. They have been shown to relieve IBS-C related symptoms [viz. constipation and abdominal pain (Love *et al.* 2014; Corsetti and Tack 2013)]. Most commonly prescribed, *Linaclotide*, has been shown safe and effective (Atluri *et al.* 2014; Wensel and Luthin 2011) with the most widely reported side effect being exacerbated diarrhoea (Yu and Rao 2014).
- v. **Antibiotics and glucocorticoids:** These two types of drugs are contextually grouped together, because, as discussed in Section 2.2.2.6, low level inflammation is observed in some IBS sufferers, especially patients with PI-IBS (Spiller and Campbell 2006). This finding supports the use of anti-biotic and/or glucocorticoid medication to treat individuals of this particular subtype (Basseri *et al.* 2011; Thebane and Marshall 2009). Although not available to the South African market, *Rifaximin* is the only antibiotic so far tested in individuals with IBS with reported claims that their quality of life has moderately improved (Pimental, Park and Mirocha 2006). Other antibiotics include *nystatin* and *tetracycline*. While available in South Africa these are, however, associated with some intolerable systemic side effects including nausea, vomiting, diarrhea, dysphagia, oral irritation and genital rash and swelling (Rezaie *et al.* 2010; Saadi and McCallum 2013). Glucocorticoids may benefit some IBS-D patients. However, this notion is based purely on the observation that patients who take these drugs previously had fewer symptoms (Huerta *et al.* 2003); further research is required to establish their role in the management of PI-IBS.
- vi. **Fibre supplements** are often preferred to dietary fibre which can cause flatulence and bloating. *Metamucil* and *Citrucel* are popular options (Lacy and Lee 2005) and although their efficacy has yet to be proven, some improvement has been described in IBS-C patients who reported amelioration of abdominal pain and constipation (Moayyedi *et al.* 2014; Freeman *et al.* 2010; Bijkerk *et al.* 2004). Many other types of fibre supplements are available – synthetic and

natural (e.g. bran or psyllium compounds) all of which can exacerbate a patient's bloating and flatulence (Lacy and Lee 2005).

- vii. **Probiotics:** As discussed in Section 2.2.2.5, the GI microbiome is widely speculated to be central to the pathogenesis of IBS (Chissard *et al.* 2007). This notion is widely supported by the successes achieved by probiotic medications (Saggiaro 2004). Probiotics are defined as “living micro-organisms that, upon ingestion in certain numbers, exert health benefits beyond those of basic nutrition” (Guarner *et al.* 2005). Although the notion of orally consuming bacteria was first described more than a century ago by the Russian, Metchnikoff, this practice has only in recent years gained credibility and received serious consideration (Sheil *et al.* 2007). Specific strains, such as *Bifidobacterium lactis* DN-173010 and the probiotic complex VSL#3 (comprised of several species including *Lactobacillus rhamnosus* GG, *Lactobacillus Rhamnosus* LC705, *Bifidobacterium breve* Bb99 and *Propionibacterium freudenreichii ssp shermanii*) have been clinically proven to alleviate bloating, distension and flatulence, while others such as *Bifidobacterium infantis* 35624 reduce bloating as well as other IBS symptoms e.g. abdominal pain or discomfort (Major and Spiller 2014; Hungin *et al.* 2013; Moayyedi *et al.* 2010; Brenner *et al.* 2009; Mullin *et al.* 2008; Quigley and Flourie 2007). Several more studies have shown probiotic therapy to be superior to placebo in the management of IBS related symptoms (Chen and Walker 2011; Romano *et al.* 2010; Ford, Talley *et al.* 2009; Brenner *et al.* 2009; Ford, Talley *et al.* 2009). Three large randomized, placebo-controlled trials confirmed the efficacy of probiotics in reducing IBS symptoms (Whorwell *et al.* 2006; O'Mahony *et al.* 2005; Kajander *et al.* 2005). These results have helped establish probiotic medication as an effective treatment option for IBS patients.
- viii. **Bulking agents** e.g. psyllium and methylcellulose bind to water to increase stool bulk and relieve constipation (Li and Li 2015). In a review on bulking agents, Jailwala *et al.* (2000) concluded that although the efficacy of these agents could not be clearly established, they did bring about relief of constipation, while having

no or little effect on other global IBS symptoms i.e. bloating and pain. Ruepert *et al.* (2011), however, found no evidence of bulking agent effectiveness in the management of IBS.

- ix. **Laxatives:** According to Shen and Nahas (2009), some osmotic laxatives (e.g. Lactulose) may lead to exacerbation/perpetuation of IBS symptoms, with associated increased abdominal pain. In the case that chronic laxative treatment is deemed necessary, polyethylene glycol (PEG) based laxative is recommended instead (Paul *et al.* 2013).

- x. **Anti-depressants**, such as tricyclics (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for all IBS subtypes, with proven efficacy for symptomatic relief of abdominal pain (Li and Li 2014; Vanuytsel *et al.* 2014; Ruepert *et al.* 2011; Ford *et al.* 2009). These drugs are particularly effective for patients with co-morbid depressive and anxiety disorders and are often used in patients with chronic refractory symptoms (Freeman 2010). TCAs are helpful in IBS-D patients due to its constipating effect, and should therefore be avoided in IBS-C cases. Conversely, SSRIs should be avoided in IBS-D patients as diarrhoea is a side effect thereof. Although SSRIs present with fewer adverse effects than do TCAs (Jackson *et al.* 2000), due to conflicting data regarding safety, efficacy and long-term outcome effects, they are not recommended in patients without co-morbid psychiatric conditions (Bundeff and Woodis 2014) and should only be considered in resistant IBS-C patients (Jackson *et al.* 2000). According to Shah *et al.* (2012), clinicians should expect one adverse effect per three patients who benefit from TCA treatment. These adverse effects most commonly include dizziness and drowsiness which negatively affect one's quality of life and therefore doctors only prescribe limited use thereof (Uher *et al.* 2009).

- xi. **Anxiolytics**, such as benzodiazepines, could be prescribed for short periods if the symptoms are stress-related (Mayer 2013). These, however, offer little long term therapeutic benefits due to habituation and often serious consequences of interaction with alcohol and other medication prescribed for this condition. Alternative non-drug measures are recommended to address anxiety which may cause or exacerbate IBS symptoms (Shen and Yaso 2009).

2.2.6.2a International Treatment Guidelines

Formal South African guidelines (The National Department of Health 2012; www.doh.gov.za) mirror those on a global level with the exception of IBS-specific drugs that have been approved in the US viz. linaclotide, tegaserod, alosetron, eluxadoline & rifaximin (Quigley et al. 2015; www.diabetessa.org.za). The WGO (Quigley *et al.* 2015) provides the following cascade of *resource*-sensitive (i.e. according to the patient's economic status) management options to guide clinicians and assist patients in decision making as to how to approach the management of this condition:

Low resource levels

- Reassurance, dietary and lifestyle review, and disease counselling.
- Symptomatic treatment of:
 - Pain, with a locally available anti-spasmodic medication; for more severe cases a low-dose tricyclic antidepressant or SSRI should be added.
 - Constipation, with dietary measures and fibre supplementation, progressing to osmotic laxatives such as lactulose.
- Address diarrhoea with a simple antidiarrheal.

Medium resource levels

- Reassurance, dietary and lifestyle review, and disease counselling.
- Add a quality probiotic.

- Symptomatic treatment of:
 - Pain, with a locally available anti-spasmodic medication; for more severe cases a low-dose tricyclic antidepressant or SSRI should be added.
 - Constipation, with dietary measures and fibre supplementation, progressing to osmotic laxatives such as lactulose.
 - Address diarrhoea with simple anti-diarrheal.

High resource levels

- Reassurance, dietary and lifestyle review and disease counselling.
- Add a quality probiotic.
- Symptomatic treatment of:
 - Pain, with a locally available anti-spasmodic; for more severe cases a low-dose tricyclic antidepressant or SSRI should be added.
 - Constipation, with dietary measures and fibre supplementation, progressing to osmotic laxatives such as lactulose.
 - Address diarrhoea with simple antidiarrheals.
- Psychological approaches (hypnotherapy, psychotherapy and group therapy) should be considered as well as consultation with a dietician.
- Where approved, add specific pharmacological agents:
 - Lubiprostone or linaclotide for IBS-C.
 - Rifaximin for diarrhea and bloating.
 - Alosetron and eluxadoline for IBS-D.

The above mentioned IBS-specific drugs are not freely available in South Africa. Second line treatment protocols in this country include the use of bile acid sequestrants (viz. cholestyramine) for IBS-D and simethicone for pain and bloating (www.diabetessa.org.za).

2.2.6.2b Patients' perspectives

The FDA (2015) conducted a survey to gain insight into patients' perspectives on the effects of FGIDs (of which IBS is the most commonly reported on) and drug therapies currently available. Below is a summary of patients' opinions of their prescribed treatment:

- Most patients reported the significant impact of treatment adverse effects. Some participants commented that adverse effects may exacerbate their condition.
- Some patients reported that their medications initially took effect, but lost effectiveness with time, as they developed tolerance to the drugs.
- Some patients divulged they gained weight which had a negative effect on their self-image.
- Patients also commented on the burden of their treatment regimens – that they often have to take several different medications daily to treat their various symptoms, and forever in the process of trying different medication options.
- Patients also mentioned the medication costs and that it is not always covered by medical aids or health care insurance providers.
- Participants of the same survey were asked to report on specific management options that they identified as “ideal”: The need for increased medical knowledge on IBS: These participants stated that ideally they would like clinicians to be able to accurately diagnose their condition so that it could be managed successfully.
- The need for effective treatment options: Participants highlighted that they would like clinicians to better address the underlying cause of the disease, offer treatments / medications in line with their level of diagnosis without the adverse effects.
- The need for faster acting medications: Participants requested quick-acting medications that could control e.g. flatulence and breaking wind, to prevent “accidents” and as such public humiliation.
- The need for a treatment protocol: These participants pointed out that they would like to be educated on better eating habits to reduce symptoms and so improve their overall health and well-being.

2.2.6.3 Psychological interventions: mind-body therapies

As previously described (Section 2.2.2), there is a significant psychological component to the postulated pathophysiology of IBS, with a substantial co-morbid occurrence of anxiety, depression, somatoform syndromes as well as post-traumatic stress disorder (PTSD; North *et al.* 2007). Mind-body therapies have become a popular means to reduce IBS symptoms. These therapies are aimed at altering behaviour traits, thinking patterns and stress responses that may cause or exacerbate IBS symptoms (Zijdenbos *et al.* 2009; Wilson *et al.* 2006). According to Grundmann and Yoon (2014), hypnotherapy and cognitive behavioural therapy (CBT) have the most evidence of clinical effectiveness in the management of IBS. Similarly, the American College of Gastroenterology (ACG) Task Force (Brandt *et al.* 2009) concluded that mind-body therapies, including hypnotherapy, cognitive therapy, dynamic psychotherapy, but *not* relaxation therapy, are more effective than conventional care in amelioration of IBS symptoms.

Hypnotherapy is defined as “an intentional induction of the hypnotic state that is achieved by various methods including deep relaxation, mental imagery, and more subtle indirect techniques” (Whorwell 2005). This hypnotic state is similar to sedation, but without the loss of consciousness, and allows for heightened senses and enhanced body function control, which in turn affects mood, pain perception, cardiovascular responses and gastrointestinal motility (Webb *et al.* 2007; Cuellar 2005; Gonsalkorale *et al.* 2004; Rainville *et al.* 1999). For example, hypnotherapists employ progressive muscle relaxation as well as suggestions of relaxation, to reduce striated muscle tension and to relax GI smooth muscle (Drossmann, Creed *et al.* 1999). Their words of suggestion may also help their patient perceive pain differently. They may also offer suggestions to alter their patients’ negative mood cycles to a more positive outlook as a coping technique to better manage their pain. These suggestions of relaxation can also be applied at home via audiotape, allowing for autohypnosis so that the patient can continue with regular home treatment. Specific gut-directed hypnotherapy sessions have been investigated in several RCTs, and the results have demonstrated that IBS patients responded positively (Gerson *et al.* 2013; Moser *et al.* 2013; Lindfors *et al.*

2012; Vlieger *et al.* 2007; Simren *et al.* 2004; Lea *et al.* 2003). Meta-analysis of these trials show that eight to twelve weekly hypnotherapy sessions can significantly improve a patient's pain, GI motility, and mood even when they are not following a medical regimen to manage their symptoms (Grundmann and Yoon 2014). In addition, several studies showed that the beneficial effects persisted for at least 10 months following treatment (Gerson *et al.* 2013; Moser *et al.* 2013; Roberts *et al.* 2006; Gonsalkorale *et al.* 2003).

Hypnotherapy, therefore, appears to be efficacious and long-lasting in improving IBS symptoms. In addition, it can serve as a valuable adjunct (or alternative) to conventional medication regimens. Moreover, Rutten *et al.* (2013) and Paul *et al.* (2013) point out that because adults seem to tolerate hypnotherapy so well, they recommend it as the first line of defence for managing IBS in children.

While hypnotherapy can directly alter the patients' perception of their IBS symptoms, *cognitive behavioural therapy (CBT)* is more aimed at empowering the patients themselves to change their thought processes and behaviour toward their disorder (Zijdenbos *et al.* 2009; Turner, Holtzman and Mancl 2007). It focuses on identifying and correcting irrational thoughts and behaviour, while employing a wide range of strategies to impart new ways of thinking, changing negative perceptions into a more positive outlook and rational behavioural response (Grundmann and Yoon 2014). In IBS, symptom aggravation often occurs when patients are overly concerned and fixated on their condition (Weinland *et al.* 2010). As with studies on hypnotherapy, several studies confirm the effectiveness of CBT in improving both the quality of life and symptom severity, particularly with regards to pain perception and co-morbid depression and anxiety (Jones *et al.* 2011; Andersson *et al.* 2011; Drossman *et al.* 2003; Boyce *et al.* 2000; Greene and Blanchard 1994). Studies comparing the use of CBT with conventional medical treatment, show that CBT not only improves pain and GI dysmotility, but also benefits patients' moods and coping strategies (Craske *et al.* 2011; Mahvi-Shirazi *et al.* 2008; Kennedy *et al.* 2006). In some of the studies the beneficial effects of CBT persisted beyond the intervention period, however, follow up studies showed that the effects waned over time. Although evidence shows that CBT is

beneficial in the treatment of IBS, Mullin *et al.* (2008) warns that clinicians must be selective as to which patients they recommend for this treatment as not all patients may benefit. Instead, they suggest a combination of CBT with conventional palliative care.

Dynamic psychotherapy requires a close patient-therapist relationship. It aims to identify any difficulties in interpersonal relationships, an understanding of which may cause the patient to perceive their condition and its related symptoms differently (Drossman, Creed *et al.* 1999).

Multicomponent treatment incorporates elements of education, relaxation therapy, biofeedback, and cognitive or psychotherapy. Studies show that it can lead to a reduction in overall symptomology as well as improved quality of health (Heymann-Monnikes *et al.* 2000; Blanchard and Schwarz 1987).

Considering the role of stress in the exacerbation and perception of IBS symptomology, *relaxation therapy* has proved to be a viable option in the management of the disease. A study conducted by Keefer and Blanchard (2001) found that relaxation response meditation was superior to the study control (viz. waitlist symptom monitoring) in the management of IBS. Significant reductions in abdominal pain, diarrhoea, flatulence and bloating were noted, with improvements persisting up to one year post intervention period.

The treatment involves a variety of methods to teach patients to neutralize the physiological consequences of stress or anxiety, the “relaxation response” being a physical state of deep rest that alters both the physical and emotional response to stress (Mullin *et al.* 2008). The most widely employed techniques include “progressive muscle relaxation training, biofeedback, autogenic training and transcendental or Yoga meditation” (Drossman, Creed *et al.* 1999).

2.2.6.4 Complementary and Alternative Medicine (CAM)

As defined by the National Centre for Complementary and Alternative Medicine, CAM “is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine”; while conventional medicine is defined as “that practiced by individuals holding medical degrees, degrees for doctors of osteopathy, and other allied healthcare workers”. Whitfield and Shulman (2009) point out that complementary and alternative medicine is used along with conventional (allopathic) medicine, while alternative is used instead of conventional medicine.

CAM is widely used for chronic health disorders, either alone or in combination with pharmacological treatment regimes (Hussain and Quigley 2006). Being faced with the challenges of managing their complex disorder, compounded by the levels of dissatisfaction voiced regarding currently available conventional medications (Koloski *et al.* 2003), the recourse to alternative treatment options is prevalent among IBS patients, with between 37 and 50% reportedly using CAM to manage their symptoms (Drossman, Morris *et al.* 2009; Hussain and Quigley 2006; Kong *et al.* 2005).

CAM practitioners are known to provide a holistic approach, i.e. they investigate physical and psychological symptoms, while allopathic doctors tend to focus purely on symptoms (Shen and Yaso 2009). The following CAM therapies have been investigated and found to be effective in the management of IBS symptomology:

Herbal medicines and oral supplements

- *Peppermint oil* is widely used for its antispasmodic properties (Alam *et al.* 2013; Ford *et al.* 2008). It has been investigated in several trials and the results of which indicate that it relieves abdominal discomfort, bloating as well as global IBS symptoms (Alam *et al.* 2013; Merat *et al.* 2010; Cappello *et al.* 2007; Liu *et al.* 1997; Rees, Evans and Rhodes 1979). It has also been recommended by the American Academy of Paediatricians for use in managing IBS in children (Brandt *et al.* 2009). Peppermint is postulated to act by blocking calcium channels and facilitating smooth muscle relaxation (Mullin *et al.* 2008, McKay and Blumberg

2006). However, patients have commonly reported heartburn as an unpleasant side-effect (Hussain and Quigley 2006).

- *Artichoke leaf* extracts is a popular digestive aid. Studies have shown that it reduces bloating, abdominal pain and cramping, as well as normalizing GI motility (Bundy *et al.* 2004; Walker *et al.* 2001).
- *Turmeric powder* (curcumin) has been known to decrease IBS symptoms and increase the quality of health in IBS patients after a treatment period of two months (Bundy *et al.* 2004).
- *Melatonin* acts to promote sleep and establish healthy sleep patterns (Chang and Lu 2009). A few trials have confirmed melatonin's efficacy in reducing global IBS symptoms and increasing the quality of life in these patients (Mozaffari *et al.* 2010; Saha *et al.* 2007; Song *et al.* 2005). The mechanism by which it modulates gut motility and sensation is postulated to be via central sympathetic and parasympathetic pathways (Bubenik 2002).
- *Iberogast* is a combination of nine herbal extracts that was originally used in Germany to treat functional dyspepsia (von Armin *et al.* 2007; Rosch *et al.* 2002). It is also known as *STW5*, and it comprises of liquid extracts from chamomile flower, bitter candytuft, angelica root, caraway fruits, milk thistle, lemon balm leaves, greater celandine, liquorice root and peppermint leaves (Simmen *et al.* 2006). It was investigated for use in IBS patients in the U.S. by Madisch *et al.* (2004) who found that Iberogast significantly improved abdominal pain and quality of life in patients with all subtypes of IBS. It is thought that Iberogast acts via the influences on serotonin, acetylcholine as well as opioid receptors in the GI tract (Simmen *et al.* 2006). It has since been recommended as a complementary

treatment for IBS by the American Council of Gastroenterology Task Force (Brandt *et al.* 2009).

- *Padma Lax* is a Tibetan preparation of extracts from laxative plants viz. rhubarb root, cascara bark and nux vomica seeds. It has been shown to significantly reduce constipation, abdominal pain and flatulence in IBS-C patients (Sallon *et al.* 2002) via postulated antagonistic activity on cholinergic receptors as antagonists which in turn reduces GI contractility (Grundmann and Yoon 2014).
- An *Ayurvedic* preparation comprising of *Aegle marmelos correa* and *Bacopa monniere* (Spanier, Howden and Jones 2003), has been shown to be beneficial particularly in IBS-D cases (Yadav *et al.* 1989).
- *Traditional Chinese Medicine* (TCM) comprises of unique Chinese herbal mixtures as well as Chinese trademarked medicines that are specifically prepared for the patient based on symptom presentation (Wang *et al.* 2008). It therefore offers a treatment strategy that provides an individualized and comprehensive management approach (Wang and Zhu 2009). In China, it has been routinely applied in the management of IBS, in both TCM as well as Western hospital settings, with widespread use alongside allopathic medicine (Zhao *et al.* 2014; Gu *et al.* 2013). In a systematic review of integrated traditional Chinese and Western medicine for IBS management, Li and Li (2015) concluded that treating IBS with an integrated approach was more successful than allopathic western medicine alone. The most extensively used and evaluated TCM for IBS appears to be Tong Xie Yao Fang (TXYF), with several trials indicating the benefits thereof in alleviating IBS-D symptoms, particularly abdominal pain, distension, flatulence and diarrhoea (Pan *et al.* 2009; Bian *et al.* 2006; Leung *et al.* 2006).

- *Homeopathy*: A Cochrane review by Peckham *et al.* (2013) produced sparse and antiquated evidence in support of the use of homeopathy in the management of irritable bowel syndrome, with two reported studies (viz. Rahlfs 1979; Rahlfs 1976) claiming positive outcomes for the use of clinical homeopathic remedy *asafoetida*.

Mechanical CAM interventions

Invasive therapies

- *Acupuncture* has become a well-known mechanical CAM intervention. Its origins are in ancient Chinese medicine and is based on the theory that channels of internal energy (Qi), better known as meridians, traverse the human body (Li, Pei and Zhou 2012). There are 360 acupuncture points along these channels. This holistic approach uses a needle to target specific acupuncture points in an attempt to promote circulation of Qi, while restoring the body's energy balance (yin and yang) which in turn maintains overall health (Wu 2010). The mechanism by which the practice may elicit GI results is via its postulated effect on endogenous neurotransmitter systems (Li and Li 2015). Studies have shown that when targeting the serotonergic, cholinergic and glutamatergic pathways in IBS patients, an increase in the endogenous opioid concentration was found (resulting in reduced visceral pain perceptions) while decreased blood cortisol levels (lowered stress levels) were also observed (Ma *et al.* 2009; Zhou *et al.* 2009; Tian *et al.* 2008, Ouyang and Chen 2004). Due to the conflicting conclusions between trials and meta-analyses conducted in China and those performed in Western countries (Manheimer *et al.* 2012; Li, Pei and Zhou 2012; Anastasi *et al.* 2009; Lembo *et al.* 2009; Schneider *et al.* 2006; Xiao *et al.* 2004) the need for further research is indicated so to evaluate the efficacy and mechanism of acupuncture.

- *Colonic hydrotherapy (CHT)* is commonly used to treat constipation and incontinence by applying a water enema to flush the colon (Chang and Lu 2009). It is important to note that the safety of this practice has not been established, with reported adverse effects including rectal bleeding, pelvic abscess, perforation and gangrene (Chang and Lu 2009; Seow-Choen 2009).

Non-invasive therapies

The following ***non-invasive manual therapies*** have been investigated for their effect on IBS related symptoms, studies of which feature in this systematic review. Although they deserve a mention in the context of mechanical CAM interventions, they shall be discussed in more detail in the next section of this chapter (viz. 2.4. Manual Therapies).

- *Yoga* (Brands *et al.* 2011; Kuttner *et al.* 2006; Taneja *et al.* 2004)
- *Reflexology* (Tovey 2002)
- *Massage* (Lamas *et al.* 2009)
- *Osteopathy* (Piche *et al.* 2014; Attali *et al.* 2013; Florance *et al.* 2012; Pizzolorusso *et al.* 2011; Brugman *et al.* 2010; Hundscheid *et al.* 2006; Gamber *et al.* 2002; Brice and Mountford 2000; Perrin *et al.* 1998)
- *Traditional Chinese Spinal Orthopaedic Manipulation* (Xing *et al.* 2013; Qu *et al.* 2012)
- *Chiropractic treatment* (Amalu 1998; Munton 1999; Wagner *et al.* 1995)

Characteristics of CAM users

Characteristics associated with patients who typically pursued CAM for the management of their symptoms include the following (Van Tilburg *et al.* 2008):

- did not respond to allopathic treatment,
- suffered from severe abdominal distension,
- scored high for anxiety, depression and somatisation,
- preferred to spend their money on non-prescription medications,
- and / or younger females with greater symptom severity.

It has been found that the recourse to CAM be more as a result of these characteristics, rather than due to dissatisfaction with more conventional medical approaches, as CAM users did not describe their prescription medications as less effective than non-CAM users (Van Tilburg 2008; Koloski *et al.* 2003). It is therefore suggested that CAM use is ultimately driven by disease severity rather than dissatisfaction with conventional medicine.

Research has indicated that more females than men tend to pursue CAM treatment (Koloski *et al.* 2003; Berman *et al.* 2000). CAM treatment is also associated with people who have higher levels of education, who prefer a more natural treatment approach to their symptoms as they lack faith in the current allopathic medications (Van Tilburg *et al.* 2008; Spanier, Howden and Jones 2003). In addition, research indicates that people often become interested in CAM treatments as a result of recommendations by family and friends (Koloski *et al.* 2003).

Van Tilburg *et al.* (2008) identified the following most commonly used CAM modalities (percentage use expressed in brackets, along with the average annual US Dollar expenditure per modality):

- any CAM (38.4% : \$240),
- ginger root (14,8% : \$40);
- massage therapy (12,6% : \$400);
- yoga (10% : \$80);
- homeopathy (8,1% : \$120);
- aromatherapy (7,2% : \$40).

They concluded that by moving CAM therapies that demonstrated effectiveness into conventional care settings, as well as providing health insurance compensation for these modalities, more IBS patients could access them. However, to achieve this, the current paucity of knowledge about treatment effectiveness needs to be addressed, as well as ensuring greater access to interventions with established efficacy for e.g. hypnotherapy and psychotherapy to a broader population of IBS patients (Van Tilburg *et al.* 2008).

A key concern for clinicians treating IBS is that some CAM interventions may provide little more than a *placebo effect*. An analysis of 31 trials investigating the use of CAM in the management of IBS, estimated the placebo response rate to be in an excess of 40% (Mullin 2001). It is noteworthy that this rate is comparable to that found in IBS patients enrolled in other medical trials (Patel *et al.* 2005; Koloski 2003). In CAM, many treatments are administered frequently and are often associated with significant patient-therapist interaction and/or physical contact, factors that are thought to increase the placebo response of these therapies (Hussain and Quigley 2006). Pitz *et al.* (2005) suggested that, in order to address and minimise this placebo effect in clinical trial settings, there should be less interaction between therapist and patient.

2.2.7 Prognosis of IBS

In most IBS patients, symptoms are likely to persist, but not worsen with time, but for some patients, their symptoms may deteriorate, while other patients will make a complete recovery. Factors that could negatively influence the prognosis of this condition include (Quigley *et al.* 2015):

- avoidance behaviour related to IBS symptoms;
- anxiety about suspected, more sinister medical conditions;
- a long history of IBS;
- impaired function as a result of debilitating symptoms;
- chronic life stresses;
- psychiatric comorbidity.

The healthcare provider involved in the management of IBS may improve the prognosis thereof firstly by acknowledging the disease, then by reassuring patients while educating them about their condition, and ultimately by designing a treatment protocol that will address not only the underlying pathological processes, but also any psychological factors that may contribute to the manifestation of their symptoms.

2.3 Non-invasive Manual Therapy

Dorland's Medical Dictionary (1994) simply describes *manual therapy* as “a skilful or dexterous treatment by hand”. However, more expansive definitions are offered by the various professions that employ this modality, often with varied descriptions and in context of what is allowed within the particular practitioner's scope of practice. Korr (1978) defined it as the “application of an accurately determined and specifically directed manual force to the body, in order to improve mobility in areas that are restricted; in joints, connective tissues or in skeletal muscles”, while a consensus study of US Chiropractors defined manual therapy as “procedures by which the hands directly contact the body to treat articulations and/or soft tissues” (Gatterman and Hansen 1994).

Manual for the purpose of this study, refers to any therapy (including motion therapy) or manipulation (including chiropractic, osteopathic, spinal and orthopaedic manipulations, applied kinesiology, acupressure, massage, reflexology and yoga) of body tissues, muscles and bones by hands or equipment to improve health and circulation, relieve fatigue so to promote healing (PubMed MeSH terms, 2016). Non-invasive for the purpose of this study, refers to any therapy that is applied to the soma (anything derived from the ectoderm of the embryo) from an external source. This definition further implies that the therapy does not involve the introduction of equipment, fluids, or other chemicals into the body (PubMed MeSH terms, 2016).

To better conceptualise the role that non-invasive manual therapies play within the scope of medicine, an understanding of their origins as well as historic development is beneficial.

2.3.1 History of manipulative therapy

Manipulative therapy has been performed for millennia and adopted by a variety of cultures worldwide [including the Balinese of Indonesia; Lomi-Lomi of Hawaii; shamans of Central Asia; sabadors in Mexico; as well as by the bonesetters of Nepal, Russia and Norway (Pettman 2007)] to treat musculoskeletal disorders. Evidence of its practice traces as far back as the Ming Dynasty era 4000 years ago (WHO 2010); ancient

Egyptian hieroglyphics (Basmajian and Nyberg 1993); ancient Thai and Japanese traditions (Bergmann, Peterson and Lawrence 1993); as well as in the folktales of Native American tribes (Leach 2004).

In ancient Western civilization, Greece is cited as the source of the first historic reference to the practice of manipulation. The detail in which the procedures were depicted in these records, may imply that the practice was well established at the time, and probably predated the 400BC reference (Pettman 2007).

The Father of Medicine, Hippocrates (460-385BC), could be considered a pioneer in the field of manipulative therapy as he was the first physician to document spinal manipulative techniques in his publication, "*Corpus Hippocrateum*" (Haldeman 2005). In it he describes rudimentary manipulative techniques and devices to apply traction to the spine, specific to the treatment of scoliosis. In addition, he details specific points of contact to which manual thrust should be applied in order to reduce a gibbus spine (i.e. a prominent vertebra)(Pettman 2007). During this era, the principles of manipulation lay in restoring normal locomotor function to ensure optimal neurological function, thereby achieving a state of health (Basmajian and Nyberg 1993). The role that manipulation plays in facilitating the body's ability to heal itself, also referred to as "innate intelligence" (Plaughter 1993), is fundamental to the "conservative ethic" approach of healing as advocated by Hippocrates (Haldeman 2005). His techniques, as well as the design of his treatment plinth, prevailed for more than 1600 years (Pettman 2007).

Claudius Galen (131-202AD), a prominent Roman surgeon, was another proponent for spinal manipulative therapy. In the early second century he wrote: "Look to the nervous system as the key to maximum health" (Pettman 2007). His techniques included treading or standing on dysfunctional spinal segments (Pettman 2007), often making reference to the works and illustrations of Hippocrates. He famously treated Eudemus (Roman academic) for the paralysis he was experiencing in his arm and hand. By adjusting his cervical spine, the paralysis was resolved (Harrison 2014).

Another significant reference to the manipulative techniques described by Hippocrates, was made in Avicenna's (980-1037AD) medical text "*The Book of Healing*" (Pettman

2007). An Arabian physician, his text not only made an invaluable contribution to advancing philosophy of manual therapy in the Middle East, a Latin translation reached Europe and future academics including Leonardo Da Vinci. This transfer of knowledge would greatly support the resurgence of the science of medicine at the end of the Dark Ages (Haldeman 2005). This revival of medicine is believed to have started with Andreas Vesalius, who contributed with a detailed description of human anatomy in 1543 (Pettman 2007).

Guido Guidi and Ambrose Pare referred to Hippocrates's manipulative techniques in their respective 16th century texts. Pare was a prominent French military surgeon, who in 1580 advocated the use of spinal manipulation to treat abnormal spinal curvatures in patients (Pettman 2007; Andersen 1983).

Notwithstanding the support of prominent medical figures throughout the ages, by the 18th century, physicians had largely discarded the use of spinal manipulation (Pettman 2007). Factors that may have contributed to this demise (and may have caused fear and apprehension in practitioner and patient alike during this time) include:

- The harmful effects of applying manipulative thrusts to spines severely weakened by tuberculosis, a disease endemic to the times (Pettman 2007).
- Practitioners fears of contracting communicable disease for example syphilis, another common illness of the era (Haldeman 2005).
- The cultic stigma (prevailing at a time when the church was instrumental in the development of medical science) attached to hands-on techniques (Basmajian and Nyberg 1993).
- Public perception that bonesetters, the manipulative therapists of the times, were not as well educated or culturally accepted as their medical counterparts (Basmajian and Nyberg 1993).

The practice of manipulation was to be marginalized to the field of traditional village healers in some areas of Europe and Asia, where bonesetters continued to achieve success in their practice, while gaining popularity among the general practice (Pettman 2007). While most of the medical fraternity scorned bonesetters and did their utmost to

keep them from practicing, there was no denying the role of manipulation as a healing art. Sir James Paget, a celebrated surgeon of his era, recognized and appraised the art of bonesetting in his article “*Cases That Bone-Setting Cures*”, which was published in the British medical Journal in 1867. He suggested that it would serve medical doctors well to observe as well as learn from bonesetters (Pettman 2007). Practices like “bleeding” and applying hot irons (cauteries) to affected areas were the order of the day. The often harmful and ineffective outcomes of these treatments, not only disheartened patients, but caused physicians to doubt their own function. Patients began to demand more accountability from their doctors (Haldeman 2005) and started to explore alternative practices that offered the Hippocratic “conservative ethic” of medicine, with the principle of “first do no harm” (Haldeman 2005). This resurgence of manual therapies led to the development of several interventions that are based on both the Hippocratic principles, as well as medical knowledge current of the times (Keating 1992). These interventions are as follows:

- **Bonesetting** comprised a therapist trained in the practice of joint manipulation or joint reduction, including the setting of fractures. Although this practice finds its origins in Central Europe (Basmajian and Nyberg 1993) reference to bonesetting has been discovered in the Americas (Basmajian and Nyberg 1993); North Africa (Gatterman 1990); as well as some regions of Asia (Gatterman 1990). It was most frequently associated with folklore and family tradition, with the healing art traditionally transferred via “father-child” apprenticeships (Gatterman 1995). The ultimate demise of bonesetting can be attributed to its conformation to conventional medical practices, as it was incorporated into the medical fraternity as the modern day branch of orthopaedics (Haldeman 2005, Gaucher-Peslherbe 1993).
- **Magnetic healing** was described as “practitioners of magnetic healing, faith healing and mental healing who often made bodily contact with their hands when treating patients” (Haldemann 2005). Specific techniques remain unclear and at best vaguely described as the application of some dynamic energy and forceful massage (Gevitz 1988).

- **Osteopathy** originated in North America in the latter part of the 1800's (Ottosson 2011; Pettman 2007). Andrew Taylor Still (1828-1917) was an unorthodox medical doctor who regarded the medical practices of the time to be more harmful than beneficial to patients. He did, however, retain his medical license, even if only to advance his novel approach to healing, a concept borne of the following personal anecdote. Still had suffered from chronic headaches throughout childhood. He fell asleep with his neck wedged between some tree roots one day and experienced relief from his headache while in this position. This observation led him to devise a theory that optimal health could only be attained through the maintenance of optimal musculoskeletal functioning (Pettman 2007), and that disease was the body's natural response to an abnormal body state (Basmajian and Nyberg 1993). He based his theories on the premise of the "disturbed artery", which described impaired blood flow as the cause for disease. This "Law of the Artery" was to become a central tenet on which the philosophy and practice of osteopathy was based (Harrison 2014; Haldeman 2005; Gatterman 1995). Still employed a long-lever technique to manipulate various spinal levels with the aim of restoring and maintaining the body's innate energy flow (Basmajian and Nyberg 1993). His conservative practice ethic soon gained recognition of the general public, becoming a popular alternative to conventional medicine. He did not, however, receive the same level of acceptance from his medical peers, remaining largely ostracized by the fraternity. His open disdain for the medical profession confounded by his *then* outrageous belief that manipulation could cure disease, prevented him from teaching his ideologies and techniques at established medical institutions (Pettman 2007). This constraint as well as the growing patient demand for osteopathic treatment, would lead Still to found the American Osteopathic College in 1892. As the profession developed, the curriculums at osteopathic schools would adopt much knowledge from their medical counterparts. The philosophical divide that had once existed between the professions, tapered with time, as osteopathy eventually aligned itself with medicine, eventually being taught as part of medical practice (Haldeman 2005). By the 1930's many

osteopaths had become fully incorporated into the medical field, practicing as osteopathic physicians. They deviated from their once conservative ethic, receiving little (if any) training in manipulative techniques. This resulted in the inevitable decline of osteopathy worldwide, although a relatively small number of osteopaths still practice true to Still's original philosophies (Haldeman 2005).

- **Chiropractic** : The father of Chiropractic, Daniel David Palmer (D.D.), was a well educated science enthusiast who, after working as a horticulturist, school teacher and farmer, became a self-trained magnetic healer who further studied spinal anatomy and manipulation techniques (Ottosson 2011; Pettman 2007). In 1895, ten years into his healing practice, Palmer was consulted by the janitor of his building. Harvey Lillard had complained to him of deafness that manifested at the same time as he strained his back, 17 years earlier, reportedly hearing a distinct “pop”. Upon physical assessment Palmer discovered a vertebral spinous process seemingly “out of alignment”. As he applied a thrust to the vertebra, Lillard’s hearing improved instantly. (Pettman 2007). This was essentially the birth of chiropractic. Palmer theorized that a malaligned vertebra would impinge on a nerve. This added pressure on the nerve would impair nerve impulse transmission, resulting in disease and/or dysfunction. This theory is known as the “Law of the Nerve” (Pettman 2007). He is widely credited for the phrase “vertebral subluxation” describing the mal-aligned vertebra (Harrison 2014; Phillips 2013; Leach 2004). However, it appears to be Dr. Johannes Hieronymi who first used the word “subluxation” when describing a spinal dysfunction in his dissertation (1746) (Pettman 2007). One of Palmer’s patients would entitle his healing art, the name of *chiropractic* was so derived from the Greek words *cheiros* (hand) and *praktos* (done by) (Chiropractic Association of South Africa 2016; Harrison 2014; Chapman-Smith 2000). The medical fraternity, as with Still before him, scorned his novel approach to disease management. Undeterred, he persevered in his practice and in 1897 opened his first college, *The Palmer College of Cure* (Pettman 2007). His son Bartlett Joshua (B.J.) would graduate from the college ten years later. Not before witnessing the arrest and prosecution

of his father, along with scores of fellow chiropractors, for practicing medicine without a license. D.D. received a sentence of 23 days imprisonment as well as a \$350 fine. In a landmark ruling that would spell the end of this anti-chiropractic campaign, one of D.D.'s graduates, Shegataro Morikubo, was found innocent based on his argument that he was not in fact practicing medicine, but the specific art of chiropractic (Pettman 2007). While D.D. promoted chiropractic education on the US West Coast, B.J. was concerned with the financial and academic development of the college, and by 1910 he had introduced the use of X-ray into the field of chiropractic (Pettman 2007). Despite the initial opposition from the medical fraternity, chiropractic gained popularity as well as scientific credibility over the years, a dynamic largely believed to be as a result of the dedication and tireless works of the Palmer's, asserting the role of the chiropractic profession in primary healthcare (Pettman 2007). The vertebral subluxations described by Palmer have since been depicted as "motion segments that show aberrant motion, alignment and/or physiological function" (Leach 2004; Gatterman 1995), with "associated biochemical changes within the segment that affect muscles, nerves, ligaments/ connective tissue and vessels, causing clinical symptoms" (Bergman and Peterson 2011). Subluxations are traditionally treated using short lever, high velocity, low amplitude thrusts (HVLATs), with the aim of restoring normal motion and alignment of a motion segment, in turn ensuring optimal physiology functioning (Leach 2004; Chapman-Smith 2000).

- **Naprapathy** is a spin-off of chiropractic developed by Oakley Smith (a former student of D.D. Palmer) in 1906/1907 (Ottosson 2011). It was based on the tenet that ligamentous contractures a.k.a. ligatights, caused the obstruction of nerves and blood vessels [also referred to as the "connective tissue doctrine" (Harrison 2014)]. The theory is that by applying stretches to these contracted ligaments via a manual thrust-like maneuver, normal neural transmission as well as blood flow can be restored (Basmajian and Nyberg 1993).

- **Massage** was reportedly the first form of manual therapy and probably began with cavemen rubbing their bruises (Tappan 1988). It is believed to have developed from traditional folk medicine, and shares many aspects with Eastern and Asian medicines. Egyptian, Japanese and Persian medical literature commonly refer to massage as a healing art form (Ottosson 2011; Tappan 1988), while Hippocrates himself studied massage, with records dating back to 430BC providing evidence that he prescribed the use of massage after manipulative treatment (Tappan 1988). Another prominent Greek physician, Asclepiades, believed that massage restored the normal flow of nutritional bodily fluids, thereby maintaining a state of health. He trusted the healing effects of massage to a point of denouncing all other forms of medicine (Tappan 1988). As Avicenna was credited with the development of manual therapy in the Middle East, similar contributions were made by the Chinese through the work of Chang Chung-King (Harrison 2014; Basmajian and Nyberg 1993). The eastern philosophy of manual therapy would lay ground for the development of disciplines such as Tuina (WHO 2010,a); Nuad Thai (WHO 2010,b) and Shiatsu (Ernst 2003).
 - *Tuina*, a Chinese form of remedial massage (Xue *et al.* 2008), has been used in China for more than 2000 years. Based on Taoist and martial arts principles that aim to harmonise the eight principles of health (as associated with Traditional Chinese Medicine). It involves the application of rubbing, rolling, kneading and/or brushing techniques to one or more areas between one or more joints (WHO 2010,a).
 - *Nuad Thai*, or therapeutic Thai massage, dates back to more than 600 years ago. An integral component of Thai culture, Nuad Thia is principally intended for the restoration or maintenance of health, although it may be enjoyed for leisure and relaxation by some (Harrison 2014; WHO 2010,b).
 - *Shiatsu*, Japanese therapeutic massage, is based on traditional Chinese manual interventions. The aim, as with Tuina, is to maintain the balance to the body's energy meridians by restoring the flow of "chi" or life energy (Ernst 2003). Pressure is applied to traditional acupuncture points on the body, either by instrument or, in the case of *Namakoshi* Shiatsu

(considered to be the authentic version of the discipline), by the hands and fingers only (Harrison 2014).

Regarding the historic development of massage in the West, record exists of Cambridge University offering lectures in massage, exercise and hydrotherapy in 1584AD (Pettman 2007). Another two centuries would pass before any of these interventions would be held in true scientific regard. It was Swedish physiologist and gymnastics instructor, Per Henrik Ling (1776-1837), who would convincingly demonstrate the physiological benefits of massage in to the medical fraternity (Pettman 2007). The Swedish massage was thereby popularized and is still today considered the classical form of massage in the West. Interestingly, although he was instrumental in augmenting the use Swedish massage as a manual therapy, Ling never actually practiced any of the strokes specific to its routine. These strokes were developed by John Mezger (1838-1909), Dutch physician and gymnastics instructor, who adopted the French terms effleurage, petrissage and tapotment which describe the different strokes (Pettman 2007). This system is still relevant today, both in practice and in theory.

The Crimean war (1854-1856) proved instrumental in establishing massage and remedial exercise within the nursing field (Pettman 2007). Florence Nightingale (1820-1910) was tasked by the British government with assessing the health status of the British army. Once there, they were not only faced with the realities of war, but under most dire circumstances, they were forced to develop rudimentary forms of remedial exercises in attempt to save the lives and limbs of injured soldiers. Although Florence and her team of nurses were never formally recognized as the pioneers for physical therapy (in the west at least), their contribution would hold much historic value. The Lady with the Lamp, as Florence was known by the soldiers, would herself become an historic icon for compassion worldwide, and the first female to establish an academic institution for nurses (Pettman 2007). Her celebrity may have somewhat contributed to the rise in popularity of massage amongst English nurses seen in the late 1800s.

James Beaver Mennell (1880-1957) made an unequivocal contribution to the advancement of manual and physical therapies (Ottosson 2011). He was a medical officer who, between 1912 and 1935, lectured massage at St Thomas's Hospital. In

1917 he produced his text *“Physical Treatment by Movement, Manipulation and Massage”*. While at St Thomas, Mennell was assisted by Swedish physiologist, Edgar Cyriax (1874-1955). Although Cyriax would later qualify as a medical doctor (Edinburgh University), it was evident that he continued to employ physical therapies, incorporating manual methods into his medical practice (Ottosson 2011; Pettman 2007). Mennell’s final publication, *“The Science an Art of Joint Manipulation”* (1952) made a significant impact on future teaching and clinical practices (Pettman 2007). He recommends thorough investigation to differentiate between spinal and visceral causes prior to receiving (patient) or applying (practitioner) spinal manipulative therapy (Pettman 2007). His approach to better refine and define potential causes of spinal pain, the *differential diagnosis*, is still fundamental in practice and theory.

2.3.2 Reflexology

Reflexology is a non-invasive CAM modality described as a Chinese and Indian system of diagnosis and treatment dating from 3000BC (Lindquist, Snyder and Tracy 2014), based on the belief that the whole body is represented in the foot (mostly on the soles of the feet), and that the internal organs can be stimulated by pressing particular areas of the foot (Lindquist, Snyder and Tracy 2014; Ernst 2009; Tovey 2002). It is performed manually with the hands and fingers of the therapist in order to stimulate specific reflex points on predominantly the feet, but also the hands, face, ears or body of the patient (Steenkamp, Scrooby and van der Walt 2012) and aimed at restoring the balance of the life force in the body to health, vitality and well-being (Lindquist, Snyder and Tracy 2014; Steenkamp, Scrooby and van der Walt 2012).

William H. Fitzgerald rediscovered reflexology from the East and brought it to the attention of the medical fraternity in the United States in 1913 calling it “Zone Therapy” (Lindquist, Snyder and Tracy 2014; Tappan 1988). It would be fellow American therapist, Eunice Ingham, who established western reflexology in its existing form. She mapped out the entire body on the feet, referring to these areas as “reflexes”(Lindquist, Snyder and Tracy 2014). A network of community-endorsed reflexologists has since developed in the West. These practitioners have remained in practice notwithstanding

periods of legal sanctions and continuous ridicule from the medical fraternity. Their belief and practice prevailed, largely driven by anecdotal accounts of the successes achieved (Kunz and Kunz 1995).

Today it is one of the most popular complementary therapies (Ernst 2009) with several RCTs demonstrating its effectiveness in managing chronic pain as well as an array of disorders ranging from asthma and sinusitis, to IBS and menopausal symptoms (Ernst 2009; Quinn, Baxter and Hughes 2008). Reflexologists postulate that malfunction of an organ or body system leads to deposits of calcium crystalline or uric acid. These deposits would in turn impinge on the nerve endings in the feet and obstruct lymphatic flow, massaging these points break down the deposits before it can be absorbed and eliminated (Lindquist, Snyder and Tracy 2014; Steenkamp *et al.* 2012; Ernst 2009).

2.3.3 Yoga

Yoga is a group of physical, mental and spiritual disciplines which originated in ancient India as far back as 3300-1900 BC (Field 2011; Singleton 2010). There is a wide variety of Yoga schools, practices and philosophies in Hinduism and Buddhism (Singleton 2010) and while traditionally a meditative and spiritual exercise, it was popularized as a system of physical exercises across the Western world in the 1980s (Singleton 2010; Burley 2000).

Yoga comprises of different poses (asanas) accompanied by specific breathing pattern to focus attention on muscle contraction and relaxation (Grundmann 2014). Physiological beneficial effects of these various yogic procedures include toning of muscle groups, stretching and relaxation of nerves, stretching of internal organs, powerful massage to the abdominal organs and muscles, improved blood and lymphatic circulation, improved spinal flexibility, massage to the spinal nerves, toning of abdominal organs and increased sympathetic tone (Field 2011; Taneja *et al.* 2004).

2.4 Systematic Reviews

Upon reflection of the literature pertaining to IBS it becomes evident that the condition's management in particular presents the practitioner and patient with a variety of challenges. Most common of these being the management protocol's impact on patient quality of life, the inconsistent effectiveness of currently recommended drug protocols, as well as the often intolerable side effects associated with the medications. Confronted by these challenges, enabled perhaps by the vast spectrum of information accessible via the internet, patients are increasingly exploring alternative options for managing IBS related symptoms. Among these alternatives, manual therapy (viz. TCSOM, osteopathy, chiropractic, yoga and massage) has shown some benefit with fewer side effects and less attenuation (Koloski 2003). The supporting research, however, remains sporadic and diverse, and compared to studies pertaining to medical interventions, is disjointed.

The significance of conveying reliable evidence to patients for better informed decision-making is of fundamental importance in effective healthcare and has become a focal area of both research and clinical practice (Bronfort *et al.* 2010). It is widely accepted that evidence-based healthcare (EBH) ensures better patient outcomes (Reilly 2004) as it aims to afford practitioners the ability to foster independent fact-based views on ever-emerging health claims. With the fast developing stock of scientific knowledge, practitioners are required to maintain flexibility and compliance to new scientifically supported approaches to managing disease. This can only be as a consequence of the actual ability to keep abreast of the influx of scientific evidence, a process which requires well-organised literature search approaches as well as the strict application of formal procedures in evaluating the literature (Bronfort *et al.* 2010).

Herein rests the relevance of systematic reviews. A type of literature review, they provide practitioners as well as patients with a comprehensive summary of current scientific evidence based on thorough literature searches and critical evaluation of studies and validity of outcome measures pertaining to the research question. This saves the practitioner from spending time on researching individual studies. An understanding of systematic reviews, and how to put them into clinical effect, is highly proposed for all health care providers (Petticrew and Roberts 2008).

2.4.1 Outline of a Systematic Review

A detailed description of the methodology of this particular systematic review is offered in Chapter 3. The study protocol was in accordance with guidelines provided by the Cochrane Collaboration (Higgins and Green 2011), widely deemed the gold standard in systematic reviewing. The Cochrane Collaboration comprises more than 31 000 healthcare specialists who systematically review RCTs of the effects of preventions, interventions and health systems (Cochrane Library 2011). The Cochrane Handbook (Higgins and Green 2011) outlines eight general steps for conducting a systematic review. These are as follows:

1. Define the review question and develop criteria for including and excluding studies.
2. Search for studies: from electronic databases to manual “hand searches” of paper articles.
3. Select studies based on specified criteria and collect data.
4. Assess the quality as well as the levels of bias in the included studies
5. Analyse data and conduct meta-analyses (where appropriate).
6. Identify and address reporting biases.
7. Summise findings, describe strengths and weaknesses of the evidence, and present results in well-described tables.
8. Interpret results and draw conclusions.

2.4.2 The Role of Systematic Reviews

Systematic reviews aim to identify, evaluate and summarise the findings of all relevant studies, thereby making the available evidence more accessible to health care providers and patients alike [Centre for Reviews and Dissemination(CRD) Guideline 2009]. They adhere to a strict scientific design based on explicitly defined methods and therefore provide reliable appraisals of interventions with valid conclusions. When conducted correctly, they are deemed the strongest form of medical evidence available to health care practitioners and patients; and aim to contribute to more informed decision making in disease management (Higgins *et al.* 2011; Wood *et al.* 2008; Moher *et al.* 2007).

Combining the results of several studies gives a more reliable and precise estimate of an intervention's effectiveness than one study alone (Juni, Altman and Egger 2001). This instils further confidence in the effect of an intervention, while ensuring the most productive use of time and resource in managing a specific condition (Mulrow 1994). As well as providing practitioners with the most current treatment options available, systematic reviews can also reveal where paucity in knowledge exists (CRD Guideline 2009), which can then be used to guide future research.

2.4.3 The Study Type Hierarchy

The table below (*Table 2.5*) presents the hierarchy of the different study types according to the level of evidence (validity of results) that they produce respectively.

Table 2.4 Levels of Evidence

Level I	Systematic reviews, meta-analyses, randomised controlled trials
Level II	Two groups, non-randomised studies (e.g., cohort, case-control)
Level III	One group, non-randomised (e.g., before and after, pre-test and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject, case-series)
Level V	Case reports and expert opinion that include narrative literature reviews and consensus statements

Note: Qualitative studies do not include a level of evidence and are generally excluded from systematic review. [Adapted from Sackett, Richardson *et al.* (1997)]

2.4.4 Study Biases

With regard to clinical study credibility, randomised clinical trials present the most reliable evidence. With enough participants, the randomisation process is expected to ensure homogeneity among participants in the intervention and the control group. In this way, differences in outcome measurements between the groups could then be reasonably inferred to be as an effect of the applied intervention. When there are defects in the design, conduct, analyses or reporting of a study, the true intervention

effect may be distorted, either over or underestimated, thereby introducing some form of *bias* (Higgins *et al.* 2011). The strength of a study design depends on its ability to minimise the different biases (Harbour and Miller 2001) as outlined in Table 2.4.

Table 2.5 Study biases that require deliberation when conducting systematic reviews (Adapted from Higgins *et al.* 2011)

BIAS DOMAIN	SOURCE OF BIAS	SUPPORT FOR JUDGEMENT	REVIEW AUTHORS' JUDGEMENT
1. SELECTION BIAS	a) Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to intervention) due to inadequate generation of a randomised sequence
	b) Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
2. PERFORMANCE BIAS	Blinding of participants and personnel	Describe all measures used, if any, to blind trial participants and researchers from the knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to the knowledge of the allocated intervention by participants and personnel during the study

BIAS DOMAIN	SOURCE OF BIAS	SUPPORT FOR JUDGEMENT	REVIEW AUTHORS' JUDGEMENT
3. DETECTION BIAS	Blinding of outcome assessment	Describe all measures used, if any, to blind outcome assessment from the knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to the knowledge of the allocated interventions by outcome assessment
4. ATTRITION BIAS	Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group, reasons for attrition or exclusions where reported, and any re-inclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data

Table 2.5 continued

(Adapted from Higgins et al. 2011)

2.4.4.1 Grey Literature

According to Mahood, Van Eerd and Irvin (2013), in order to produce the most inclusive summary of the available literature and to increase the value of systematic reviews, “grey literature” should not be excluded from these literature reviews. This systematic review includes one study which was reported as grey literature viz. a non peer reviewed dissertation (Munton 1999). This study, although available in electronic format, was published only in its institutional repository, and since the researcher had knowledge of its existence, it was not sourced via electronic database searches, but by means of hand search (DUT Steve Biko Library Dissertation) instead. The incorporation of “grey literature” may present systematic reviews with the following biases:

- a) “Publication bias” (Dickersin *et al.* 1994) due to the fact that this type of literature may often not be peer reviewed. In some circumstances, the literature may not have received journal publication, but rather exist in the format of a thesis or another form of academic publication.
- b) “Language bias” (Dickersin *et al.* 1994) is an issue when studies are excluded based on language restrictions, imposed either by the review design, the aptitude of the reviewer, or both.
- c) “Sensitivity and precision of searching” (Dickersin *et al.* 1994). To ensure the inclusion of “grey literature”, search terms would need to be adjusted in a way that would encompass a wider pool of knowledge. The influence of search terms on a systematic review (Dickersin *et al.* 1994) can introduce certain bias. Using several types of search terms may curtail this effect (Cook *et al.* 1995).
- d) The aptitude of the researcher in applying the appropriate search terms and selection strategies (Harrison 2014).

2.4.4.2 Reporting on Study Biases

This systematic review is an academic exercise, under the guiding principles of DUT Faculty of Health Sciences Research Committee (FRC) as so determined by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (www.prisma.org). These guidelines provide two options for reporting on the various forms of biases that may present in different types of studies. One is to apply the Cochrane based tool for risk assessment (Higgins *et al.* 2011), the other requires a more narrative approach of discussing reviewed articles contextually. The latter method is presented in Chapter 4 of this dissertation, with blinding techniques reported on in the tabulated analyses of each individual study, while various risks of biases are elaborated on as 'limitations' of the studies. This method of risk assessment was collectively elected by the DUT Department of Health Sciences FRC when systematic reviews of clinical trials were first considered as research topics for Masters level dissertations.

2.4.5 Systematic review of randomised clinical trials (RCTs)

Maher *et al.* (2011) appraised the function of the PEDro Scale (www.pedro.org.au, 1999: Appendix E) as a quality measure in the systematic review of RCTs. The separate rating scales that comprise the PEDro achieved a "fair to substantial" score, while the global PEDro Scale reliability score achieved a rating of "fair to good". These findings proved the PEDro Scale to be a sufficient measure of quality, supporting its use in the systematic review of RCTs.

The scale includes the following eleven criterion categories, each to be applied in order to appraise the methodological exactitude of the RCT under appraisal. These are detailed in Chapter 3 of this dissertation.

2.4.6 Systematic review of non-randomised controlled trials (nRCTs)

The Newcastle-Ottawa Quality Assessment Scale [NOS (Wells *et al.* 2011: Appendix G)] is widely employed in the systematic analysis of nRCTs. There are, however, conflicting reports amongst various experts as to the validity of this assessment scale. Stang (2010) questioned its cogency noting that the validity of the NOS remains largely unidentified, whereas the Cochrane Collaboration (Higgins and Green, 2011), as well as Deeks *et al.* (2003), endorse the role of the NOS as a sufficient, reliable and user-friendly measure of quality for the review of nRCTs. Wells *et al.* (2003) concurred as they described the NOS as a validated measure with strong inter-reviewer reliability (with an interclass coefficient of 0.94). The NOS has been subjected to continuous review and modification (Hartling *et al.* 2012; Wells *et al.* 2003) in order to validate its capacity as gold standard measure of quality in the review of nRCTs. The scale is comprised of eight separate *items*, and is described in further detail in Chapter 3.

2.4.7 Systematic review of case reports and observational studies

The Method for Evaluating Research and Guideline Evidence (MERGE) was established by the Cochrane Collaboration, the New South Wales Health Department as well as individuals including epidemiologists and clinicians (Liddle *et al.* 1996). This system was in turn used to develop a standardised and clear method to systematically appraise the quality of evidence delivered by case reports and observational studies, giving birth to the Liddle Scale (Liddle *et al.* 1996: Appendix I), a checklist adopted by the Scottish Intercollegiate Guidelines Network. The Liddle Scale is used to ascertain the overall quality of the case reports included in the study, based on strong epidemiological principles. The relative significance of each source of bias and the degree to which these biases may jointly affect the results of the studies under review is determined by applying the set of criteria that will be described in detail in Chapter 3 along with the abovementioned scales.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter depicts the methodology that was applied to obtain and evaluate the data for this study. The methodical steps included: a thorough literature search, classifying the study selection, applying the defined inclusion and exclusion criteria, appraising the eligible publications, assessing the reviews as well as collating the results. The applied methodology is representative of the recommendations by Cook, Sacket and Spritzer (1995), Greenhalgh and Peacock (2005), and Liberati *et al.* (2009), and formed the basis upon which this research was approved by the Durban University of Technology's Faculty of Health Sciences Research and Higher Degrees Committee.

3.2 Research Design and Overview

This study took the form of a systematic review of the literature relating to the efficacy of the non-invasive ¹ manual ² therapies used for the treatment of IBS. It entailed the systematic and methodical search for all publications pertinent to the topic as depicted in the title of this study. This was primarily done via an electronic database; after which a hand search was performed (Greenlagh and Peacock 2005). The publications that were identified as eligible for this study were then categorised according to their particular study type (viz. randomised clinical trials, non-randomised clinical trials and case studies/reports) (Cook, Sacket and Spritzer 1995) and subsequently remitted to the reviewers. Different assessment scales have been developed specific to the various categories viz. PEDRO (www.pedro.org.au 2011) (Appendix E), Newcastle-Ottawa (Wells *et al.* 2011) (Appendix G) or Liddle scales (Liddle *et al.* 1996) (Appendix I). The

¹Non-invasive for the purpose of this study refers to any therapy that is applied to the soma (anything derived from the ectoderm of the embryo) from an external source. And this definition further implies that the therapy does not involve the introduction of instruments / fluids / other chemicals into the body (PubMed MeSH terms, 2016).

²Manual for the purpose of this study refers to any therapy (motion therapy) / manipulations (including chiropractic, osteopathic, spinal and orthopaedic manipulations, applied kinesiology, acupressure, massage) of body tissues, muscles and bones by hands or equipment to improve health and circulation, relieve fatigue, promote healing (PubMed MeSH terms, 2016).

six reviewers recruited to participate in this study, along with the researcher, were assigned the duty of reviewing the categorised publications. This entailed the analyses of methods employed in each of the reviewed studies, as well as grading the publications in accordance with their appropriate rating scales to ultimately assess the rigour of the methodology employed in each publication (Cook, Haynes and Mulrow 2004).

Each of the articles was reviewed by the researcher as well as 2 independent reviewers. Appropriate rating scales were employed to score each article for its methodological rigour. The results were then tabulated and remitted to the researcher, who subsequently compared the scores to ascertain the level of consensus between these individuals. Majority consensus scores allowed for the ranking of the publications by the researcher in order to determine the level of evidence provided (Moher *et al.* 1999; Kleijnen *et al.* 1997; Colditz *et al.* 1989). These results then allowed the researcher to describe the collective level of effectiveness for each of the investigated interventions (Dagenais and Haldemann 2011).

3.3 The Research Question

The research question: What level of evidence exists to support the use of non-invasive manual therapies in the management of IBS? The aim of this study was to collect, critically assess, appraise and evaluate the clinical evidence available in the literature. This to ultimately determine the effectiveness of non-invasive manual therapies in the treatment of IBS related symptoms.

3.4 The Research Methods

The methods employed in this research study were formulated to best present the following:

- A clear study question,
- Clear conceptual or decision making contexts,
- Detailed and clear descriptions:
 - Describing explicit selection criteria for studies
 - Describing explicit report criteria for evaluating the studies,
 - Describing and acknowledging known biases,
 - Describing the validity of the assessment criteria,
 - Describing the application of the criteria to assess the validity to all the studies and
 - Transparency of reporting on results.

3.4.1 The Research Procedure

Herewith a synopsis of the procedure followed (Creswell, 2009; Moher *et al.* 2007; Liddle *et al.* 1999):

- The systematic search of several electronic data bases using key terms
- This located all relevant citations pertaining to non-invasive manual IBS therapies (Appendix A).
- The citations gathered then required abstract screening (as per inclusion and exclusion criteria of the study).
- Once pertinent abstracts were included, full text publications were sourced.
- A hand search was then performed to determine whether any publications had been omitted.
- Once a composite list of all publications was compiled, the publications were categorised according to study type (Viz. RCTs, nRCTs, case studies and reports) and each reviewed by three different individuals using appropriate standardized rating scales (PEDro Scale 2011; Verhagen *et al.* 1998). Reviewer

feedback was then compared by the researcher. Majority consensus allowed for ranking of the publication by scale parameters and linked to the outcomes of the publication, in order to determine the level of evidence provided by the publication. This in turn allowed the researcher to state the effectiveness of the interventions and make suggestions for future research (Dagenais and Haldeman 2011).

Electronic data bases were initially searched for studies investigating the efficacy of non-invasive manual therapeutic methods for the treatment of IBS (see Appendix A). These data bases included PubMed, Ebscohost, Medline, CINAHL, Proquest, Health Source, Sport Discus, Science Direct, Springer Link and Summons as well as Google Scholar. Each database was searched using the keywords listed under the inclusion criteria below. An example of the method used for this search is depicted in Appendix B.

After the deletion of articles that were repeated amongst the above databases and therefore duplicated, and narrowing in on “human” studies, a total number of 1542 citations remained eligible (Appendix B – see manual therapy text box).

Following this, the citations, abstract and key words were assessed for *inclusion* criteria.

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1) INCLUSION CRITERIA

I. Citation Inclusion

- a) Title needs to include one or more of the following term(s).

Keywords: irritable bowel syndrome, conservative, manual, manipulation, manual manipulation, osteopathic manipulation, chiropractic manipulation, manual therapy, movement therapies, physical therapies, massage, exercise, kinesiology, reflexology and yoga (alone and in combination).

II. Full abstract / publication inclusion criteria

- a) Studies are English or have been translated to English.
- b) Randomised controlled clinical trials, non-randomised clinical trials, non-controlled studies (e.g. cohort) case reports/series and observational studies will all be included in the study, irrespective of randomisation or control.
- c) Studies pertaining to the non-invasive manual therapy of IBS (as per the key terms above).

Thirty-eight abstracts endured screening for the above inclusion criteria, 23 of which fell short of the following exclusion criteria:

2) EXCLUSION CRITERIA

- a) Non-English studies.
- b) Studies not accessible in full article format
- c) Studies defined as a systematic review, review of literature or expert opinions (Creswell, 2009).

This process produced a composite master list of 15 eligible publications (Figure 3.1; Appendix B). The list was expanded on by another 3 articles following a secondary search i.e. *hand search* (Appendix C) which included:

1. All studies whose citations were referenced in the full text articles accessed by the researcher.
2. Additional works by authors identified in the reference lists of those studies found in the primary search.
3. Publications recommended for inclusion by the participating reviewers.
4. Dissertations sourced from the DUT Steve Biko Library.

Once publication saturation was reached, all the eligible publications were accessed in their full article form, screened for eligibility and finally categorised according to their respective study types (viz. RCTs, nRCTs, case and observational studies). Any publications that were not directly available to the researcher during the full article search, were retrieved by Ms Finlayson (DUT Steve Biko Library) via inter-library loans (Finlayson 2016).

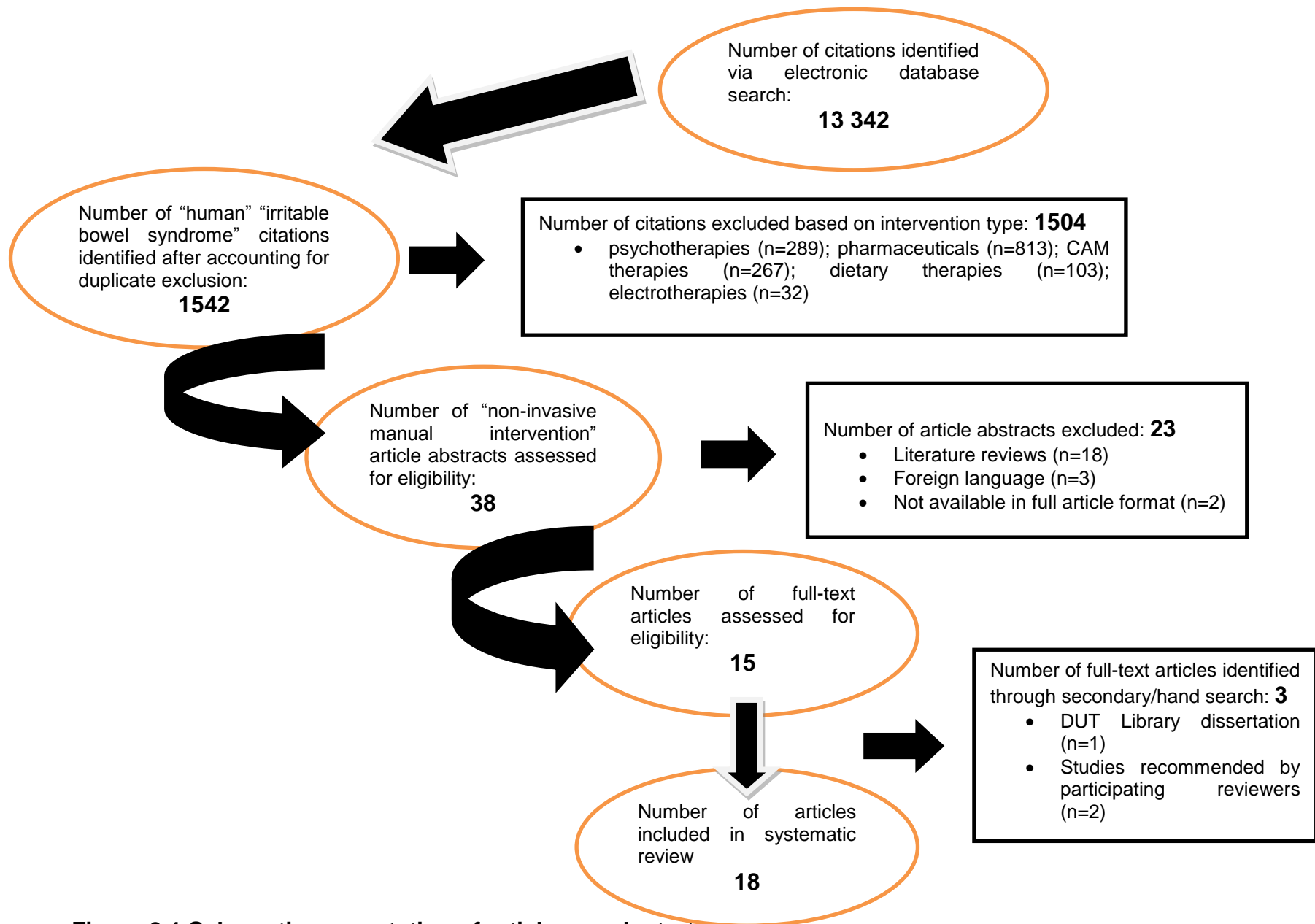


Figure 3.1 Schematic presentation of article search strategy

(Adapted from Liberati et al. 2009; Moher et al. 1999)

3.4.2 Reviews

Publications were systematically categorised according to the following study types, which in turn defined which of the validated rating scales would be employed in the rating of the individual studies, so prescribed by the Cochrane Collaboration (2011).

- a) *Randomised controlled clinical trials/controlled clinical trials (RCTs)*, as defined by the NICE glossary (www.nice.org.uk), are studies in which a number of similar participants are randomly assigned to two or more groups (via a process of randomisation) to test a specific drug, treatment or intervention. The experimental group has the intervention under trial, while the comparison or control group has either an alternative or dummy intervention (placebo) or no intervention at all.

The PEDro scale is used to assess the methodological rigour of this study type. (www.pedro.org.au 2011; Appendix E)

- b) *Non-randomised clinical trial publications* share the criteria as described for RCTs, however do not ascribe to a randomisation process. These types of studies are rated by the Newcastle-Ottawa scale (Wells *et al.* 2011; Appendix G)
- c) *Observational Studies* see the researcher methodically observing the behaviour of the participant/s, without any influence or interference from the researcher on the observed behaviour (Shaughnessy *et al.* 2005). These types of studies are best assessed by the Liddle scale (Liddle *et al.* 1996; Appendix I).
- d) *A case report or case series* reports on a small group of individuals (case series) or an individual (singular report) in a specific context, with its conclusions limited to the individual(s) and the specific clinical scenario. The focus of such research is usually a cause-effect relationship (Cassell and Symons 2005). The Liddle scale (Liddle *et al.* 1996; Appendix I) is applied to rate these studies.

Once categorised, each publication was paired with its appropriate scale and remitted to the individual reviewers for rating.

3.4.3 Reviewers

Six independent reviewers were recruited for participation in this systematic review (Please refer to Appendix D). They were required to sign a Memorandum of Agreement (MoA) (Appendix K) which detailed the process of the systematic review while defining the capacity and responsibility of each reviewer.

The reviewers were selected based on the following:

- Their qualifications, to ensure an appropriate mix of academic, clinical and research experience existed for each of the review group pairs.
- Their previous involvement in systematic reviews and publications and / or supervision experience.
- Their geographic origin, so as to be representative of various regions internationally.

The panel of reviewers consisted of the following members:

- Reviewer One: PhD -Researcher and academic (Sweden).
- Reviewer Two: PhD - Director of teaching, co-ordinator of post-graduate studies (Australia).
- Reviewer Three: PhD - Adjunct professor of Chiropractic (Australia).
- Reviewer Four: M.Tech: Chiropractic –education, clinical, research (England).
- Reviewer Five: M.Tech: Chiropractic –clinical, research, previous systematic review experience (South Africa).
- Reviewer Six: M.Tech: Chiropractic –clinical, research, previous systematic review experience (South Africa).
- Reviewer Seven (Researcher): B.Tech: Chiropractic (South Africa).

Table 3.1 Reviewers' qualification and experience levels

	Research Experience	Highest qualification		Clinical Experience	Academic Experience
		Masters	PhD		
Reviewer 1	X		X	X	X
Reviewer 2	X		X	X	X
Reviewer 3	X		X	X	X
Reviewer 4	X	X		X	X
Reviewer 5	X	X		X	
Reviewer 6	X	X		X	
Reviewer 7					

The appointment of reviewers, as per the Memorandum of Agreement (Appendix K), was a confidential process. To ensure the anonymity of the reviewers (as well as their review feedback), these reviewers were not linked with their publication groupings in the dissertation (Mouton, 1996). In addition, the reviewers were asked to refrain from discussing their allocated publications with others throughout the duration of the review procedure.

Once each reviewer had reviewed all their respective publications, data sheets were collected by the research supervisor (this data could not be accessed by the researcher until the researcher had completed her reviews – as these needed to be independent). In addition, the researcher further assessed each of the 18 publications for blinding methods and clinical outcomes. Findings were presented in tabulated format (Harris 2013), followed by a narrative depiction of methodological strengths and/or flaws, and the various forms of study biases that are observed in the different studies. The study then generated a summation of the assembled data on individual studies as well as cumulative findings pertaining to the role of each intervention in the management of irritable bowel disease, as well as a discussion with recommendations for future studies (Moher *et al.* 2015).

3.5 Data extraction process

As aforementioned, the measurement tools employed in this study (Viz. PEDRO, Newcastle-Ottawa and Liddle scales) are so prescribed by the Cochrane Collaboration (2011), the gold standard as far as systematic reviews of clinical evidence are concerned. Evidence does nevertheless suggest that these standardised rating scales have significant limitations (Moher *et al.* 1999; Moher *et al.* 1995) and lacked rigour in their development (Moher *et al.* 1999; Moher *et al.* 1995). In addition, they are not consistent in complexity, size or level of development (Moher *et al.* 1999).

The following rating scales were employed to rank publications according to their respective study subtype:

Table 3.2 Study Types and Rating Scales

Study Scales:	
Study Type:	Scale:
Randomised controlled trials/controlled trials	PEDro scale (www.pedro.org.au 1999) Appendix E
Non randomised intervention publications	Newcastle-Ottawa scale (Wells <i>et al.</i> 2011) Appendix G
Observational publications	Liddle scale (Liddle <i>et al.</i> 1996) Appendix I
Case publications/case reports	Liddle scale (Liddle <i>et al.</i> 1996) Appendix I

3.5.1 Systematic review of randomised controlled trials (RCTs)

Maher *et al.* (2003) appraised the function of the PEDro scale (www.pedro.org.au 1999) as a quality measure in the systematic review of RCTs. The separate rating scales that comprise the PEDro achieved a “fair to substantial” score, while the global PEDro scale reliability score achieved a rating of “fair to good”. These findings proved the PEDro scale to be a sufficient measure of quality, supporting its use in the systematic review of RCTs. Consequently, the PEDroScale (www.pedro.org.au, 1999) was applied to review the RCTs in this particular study. The scale includes the following eleven separate criterion categories, each applied in order to appraise the methodological exactitude of the RCT under appraisal, as adapted from Harrison (2014):

1. A description of the inclusion criteria / selection of participants.
2. A description of how the patients were allocated.
3. A description regarding the concealment of allocation.
4. A description on how the study groups were reported in terms of baseline similarities or differences, with particular emphasis on prognostic indicators / factors.
5. A description on blinding of all participants.
6. A description on blinding of therapists.
7. Whether or not the assessors were blinded.
8. At least one key outcome measure was completed by the majority (85%) of all participants.
9. All participants, who received treatment, were allocated to the control group. In the event that this was not the case, data for at least one outcome was analysed by “intention to treat”.
10. Statistical comparisons (for at least one key outcome) are reported.
11. The study provided point measures (measure of the size of the treatment effect). Including measures of variability (standard deviations, standard errors, confidence intervals, inter-quartile ranges / quartile ranges and ranges) for at least one key outcome.

A maximum score of “one” point is awarded for each fulfilled criterion point, conversely, a zero score is awarded for every unfulfilled criterion point. This will result in an overall score ranging from minimum zero to maximum eleven, with the latter score indicating the highest possible level of methodological precision, while a score of zero would indicate the lowest possible levels of objectivity. For this particular study, a mean score per study will be calculated from a minimum of three reviewers.

3.5.2 Systematic review of non-randomised controlled trials (nRCTs)

The Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al. 2003, Appendix G) is widely employed in the systematic analysis of nRCTs. There does, however exist conflicting reports amongst various experts as to the validity of this assessment scale. Stang (2010) questioned its cogency noting that the validity of the NOS remains largely unidentified, whereas the Cochrane Collaboration (Higgins and Green 2011), as well as Deeks *et al.* (2003), endorse the role of the NOS as a sufficient, reliable and user-friendly measure of quality for the review of nRCTs. Wells et al. (2003) concurred as they described the NOS as a validated measure with strong inter-reviewer reliability (with an interclass coefficient of 0.94). The NOS has been subjected to continuous review and modification (Hartling *et al.* 2012; Wells *et al.* 2003) in order to validate its capacity as gold standard measure of quality in the review of nRCTs.

In this particular systematic review, all the nRCTs were appraised utilising the NOS. The scale is comprised of eight separate *items*, each subdivided into three different *categories* (viz. *selection*, *comparability* and *exposure*) each with their own criteria as follows as adapted from Harrison (2014):

1. *Selection*: Comprises of criteria on the case definition, representativeness of the cases, the selection of controls (viz. community controls, hospital controls or no description) as well as the definition of the controls.
2. *Comparability*: Establishes how analogous the separate subject groups prove to be with respect to their baseline characteristics as well as ensuing differences.

3. *Exposure*: Contrast examines the “ascertainment of exposure” and the manner in which it is evaluated.

One point, or star, is awarded when the criterion is fulfilled. With the exception of the *comparability* category, where three options are available with two points being awarded, each of the eight items calls for one of three (either a, b, or c) responses. One point, or star, is awarded per item, with a maximum score totalling nine points, or stars.

An average of more than two reviewers, in the case of this particular study it would be three, is then calculated. This mean score assigned by the reviewers suggests the methodological rigour of the appraised study. A mean score of nine indicates the highest level of methodological rigour, whereas a score of zero notes the opposite.

3.5.3 Systematic review of case reports and observational studies

The Method for Evaluating Research and Guideline Evidence (MERGE) was established by the Cochrane Collaboration, the New South Wales Health Department as well as individuals including epidemiologists and clinicians (Liddle *et al.* 1996). This system was in turn used to develop a standardised and clear method to systematically appraise the quality of evidence delivered by case reports and observational studies, giving birth to the Liddle Scale (Liddle *et al.* 1996, Appendix I), a checklist adopted by the Scottish Intercollegiate Guidelines Network.

The Liddle Scale was employed in this particular systematic review to ascertain the overall quality of the case reports included in the study, based on strong epidemiological principles. The relative significance of each source of bias and the degree to which these biases may jointly affect the results of the studies under review was determined by applying the following set of criteria, which ultimately comprises this scale:

1. An adequate description of subjects / participants, in terms of time, place and person.
2. Drop outs in terms of
 - a. Refusal to participate,

- b. Exclusion and
 - c. Percentage of loss to follow-up.
3. Measurement of outcomes and their standardisation, validity and reliability.
 4. Measurement of outcomes for the intervention / treatment and control group / natural history group.
 5. Extraneous factors (excluding the controlled intervention), are homogenous between the various groups. If not, were these factors accounted for in the analysis?
 6. If the analysis is by intention to treat or not (note that this criterion applies to case studies / series only).
 7. If there is a multi-centre study: are the groups homogenous between the centres.
 8. Have all forms of bias been minimised?
 9. Were there any practical / ethical or other issues that prevented an RCT from being run?
 10. What was the overall effect of study (viz. the result of the tested intervention).

(Adapted from Harrison 2014)

The strength of methodological rigour, as per criterion point, was ranked in declining order viz. A, B1, B2, C or I. The award of an “A” indicating the best possible methodological rigour, while “I” indicates the worst possible methodological rigour. Where a particular criterion did not apply to the particular case study or report, the term “not applicable” (n/a) was applied.

3.6 Statistical analysis

Analysis of articles by outcome: Majority consensus rankings were utilized to rank the studies. The ranking was linked to the outcomes obtained by each of the studies, while the researcher delivered a tabulated analytical report (Harris 2013) on the various methods employed in each study. This determined the characteristics of the higher versus lower ranked studies in terms of the methodological rigour and clinical effectiveness/efficacy in order for the researcher to be able to summarise clinical applicability.

The nature of IBS poses a challenge even to researcher of the disorder. Given the fact that it is classified as a FGID, no objective markers exist to monitor changes in symptoms. As a result, IBS studies lack objective measurement tools, instead employing a range of various subjective outcome measures. This lack of consistency in reporting outcomes not only hampers the ability to comprehensively evaluate results achieved in various studies, but also prevents meta-analyses. Meta-analysis requires at least one objective measure as well as one subjective measure that is universally applied in all the studies under review, this to ensure that analyses of data across the studies are comparable. For the purpose of a masters' level dissertation, a systematic review was deemed an adequate enough academic exercise by the DUT Health Science Faculty Research Committee.

CHAPTER FOUR

RESULTS

4.1 Introduction

This chapter depicts the results of the overall review process as well as the data obtained from the reviewed publications. These data are tabulated and grouped consecutively for randomised controlled trials (n=13; Tables 4.2-4.27), followed by non-randomised controlled trials (n=3; Tables 4.29-4.34) and case studies / case reports (n=2; Table 4.36-4.39).

At the beginning of each study type section, a summary table provides an overview of the various articles within that section and indicates which tables are relevant to which article(s).

Each article that was analysed is represented by two tables:

- The first table represents a summary of the quantitative reviewer feedback (e.g. Table 4.2) from the scale utilised to assess the methodological rigour of the article under discussion. This analysis assessed predominantly the internal factors or structural factors of the research design, methodology and analysis.
- The second table (e.g. Table 4.3) presents a qualitative analysis of the same article by presenting and interrogating the following article properties: forms of measurement, frequency of measurement, duration of the study, number of participants, blinding of research personnel, whether a control has been used and randomisation of the participants. These extracted properties are discussed with a view to identifying both internal and external factors that may have affected the methodological rigour of the study. Therefore, the determination made under this section of the discussion includes both the reviewers' quantitative analyses as well as the qualitative evaluation of the article culminating in an overall evidence evaluation.

In this context the overall evidence evaluation is the determination made as a result of this systematic review indicating the level of evidence that the article, as a whole, contributes to the role of non-invasive manual therapies in the management of IBS.

4.2. Data

4.2.1 Primary data

After the primary and secondary searches were completed for this study, a final list of 18 articles was compiled.

This final list of articles was categorised according to study types (viz. RCTs, nRCTs, case studies and reports) then divided among the seven reviewers such that each article had three reviewers allocated to it. The articles were then reviewed and rated according to the appropriate rating scales described in section 3.5 of Chapter 3. Reviewer's feedback was systematically presented in tabulated form. (Tabulated Feedback Data Table- Harris 2013), with the feedback from each individual reviewer displayed as an individual ranking, along with a majority ranking (reported as the majority outcome from the three reviewers) and a percentage of agreement (determined from the total of the scores displayed in the majority column).

The percentage agreement was calculated for each individual criterion for each scale and thus represents the agreement between the reviewers for each specific criterion. Therefore, when all three reviewers agreed, a 100% percent agreement was recorded. By contrast, when all reviewers disagreed, a 33% percent agreement was calculated.

From these percentages an overall percentage agreement for the study was calculated. In this context, the overall study percentage represented the degree of cohesiveness between reviewer responses. Literature indicates that a study with a 70% or more percentage agreement (Liberati *et al.* 2009), is one in which the overall study is deemed to have a good level of methodological rigour which was well presented and clear; allowing for uniform identification and understanding of the required criteria by the reviewers.

4.2.2 Secondary data

Secondary data were used to gain further knowledge on the topics of irritable bowel syndrome, manual therapies and systematic reviews. This information was accessed via a number of sources; these data types included books, commentaries, referenced journal articles and systematic reviews. The largest amount of information was obtained from on-line articles, as well as articles sourced through the Durban University of Technology (DUT) library. Additional information was obtained through books available at the DUT library.

4.3 Abbreviations

CS:	Case study / series (case report)
F:	Female
FAP:	Functional Abdominal Pain
FBDSI:	Functional Bowel Disorder Severity Index
FSS:	Functional Somatic Syndrome
GSRS:	Gastrointestinal Symptom Rating Scale
HAD:	Hospital Anxiety and Depression
HAS:	Health Assessment Sheet
IBS:	Irritable Bowel Syndrome
M:	Male
NOS:	Newcastle Ottawa Scale
n-RCT:	Non-randomised clinical trial
n-RCTs:	Non-randomised clinical trials
OMT:	Osteopathic Manipulative Therapy
RCT:	Randomised clinical trial
RCTs:	Randomised clinical trials
SMT:	Spinal Manipulative Therapy
TCSOM:	Traditional Chinese Spinal Orthopaedic Manipulation
VAS:	Visual Analogue Scale

4.4 **Results**

The results are divided into randomised controlled trials, non-randomised clinical trials and case studies / case reports. Each section offers a small introduction followed by a summary table providing an overview of the studies which is subsequently discussed in more detail.

4.4.1 **Randomised clinical controlled trials**

The PEDro Scale (www.pedro.org.au, 1999; Appendix E) was applied to review the thirteen RCTs included in this systematic review. In short, this scale consists of eleven criteria, by which the reviewers rate the article. A total of one point is allocated to each valid criterion, with a maximum ranking of eleven.

Table 4.1 List of table numbers for RCTs in alphabetical order

Tabulated feedback data:	Analysis of article:	Author(s):	Year:	Title:
Table 4.2	Table 4.3	Attali T; Bouchoucha M; Benamouzig R.	2013	Treatment of refractory irritable bowel syndrome with visceral osteopathy: Short-term and long-term results of a randomized trial
Table 4.4	Table 4.5	Brice C. and Mountford R.	2000	A study into the efficacy of osteopathic treatment of irritable bowel syndrome
Table 4.6	Table 4.7	Florance B.M; Frin G; Dainese R; Nebot-Vivinus M.H; Barjoan E.M; Marjoux S; Laurens J.P; Payrouse J.L; Hebuterne X; Piche T.	2012	Osteopathy improves the severity of irritable bowel syndrome: a pilot randomised sham-controlled study
Table 4.8	Table 4.9	Gamber R.G; Shores J.H; Russo D.P; Jimenez C; Rubin B.R.	2002	Osteopathic manipulative treatment in conjunction with medication relieves pain associated with fibromyalgia syndrome: Results of a randomised clinical pilot project

Table 4.10	Table 4.11	Hundscheid H.W.C; Pepels M.J.A.E; Engels L.G.J.B; Loffeld R.J.L.F.	2006	Treatment of irritable bowel syndrome with osteopathy: Results of a randomized controlled pilot study
Table 4.12	Table 4.13	Kuttner L; Chambers C.T; Hardial J; Israel D.M; Jacobson K; Evans K.	2006	A randomised trial of yoga adolescents with irritable bowel syndrome
Table 4.14	Table 4.15	Lamas K; Lindholm L; Stenlund H; Engstrom B; Jacobsson C.	2009	Effects of abdominal massage in management of constipation- A randomised controlled trial
Table 4.16	Table 4.17	Munton R.	1999	The efficacy of spinal manipulation in the management of irritable bowel syndrome
Table 4.18	Table 4.19	PicheT;Pishvaie D; Tirouvaziam D; Filippi J; Dainese R; Tonohouhan M; DeGalleani L; Nebot-VivinusM.h; Payrouse J.L. and Hebuterne X.	2014	Osteopathy decreases the severity of IBS-like symptoms associated with Crohn's disease in patients in remission
Table 4.20	Table 4.21	Qu L; Xing L; Norman W; Chen H; Gao S.	2012	Irritable bowels syndrome treated by traditional Chinese spinal orthopedic manipulation
Table 4.22	Table 4.23	Taneja I; Deepak K.K; Poojary G; Acharya I.N; Pandey R.M; Sharma M.P.	2004	Yogic versus conventional treatment in diarrhea-predominant irritable bowel syndrome: A randomised control study
Table 4.24	Table 4.25	Tovey P.	2001	A single-blind trial of reflexology for irritable bowel syndrome
Table 4.26	Table 4.27	Xing L; Qu L; Chen H; Gao S.	2013	A clinical observation of irritable bowel syndrome treated by traditional Chinese spinal orthopaedic manipulation

Table 4.2	Tabulated feedback data of Article 1: PEDRO Scale					
AUTHOR(S):	Attali T; Bouchoucha M; Benamouzig R.					
YEAR:	2013					
TITLE:	Treatment of refractory irritable bowel syndrome with visceral osteopathy: Short-term and long-term results of a randomized trial					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	No	Yes	Yes	66%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	No	Yes	Yes	66%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	5/11	7/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				94%

Table 4.3 Analysis of Article 1

AUTHOR(S):	Attali T; Bouchoucha M; Benamouzig R.							
YEAR:	2013							
TITLE:	Treatment of refractory irritable bowel syndrome with visceral osteopathy: Short-term and long-term results of a randomized trial							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Rankin g out of 13	Total Percentage Agreement
1. Daily Symptom Diary : VAS	Abdominal symptoms recorded daily for the 12 week duration of the trial. Measures 2, 3 and 4 recorded at the following 3 intervals: One week before commencing treatment (EV1); week 5 (EV 2); week 11 (EV 3) and one year after week 10 (EVf). Measures 5 and 6 recorded at: EV1; EV 2 and EV3.	2 week run-in period 10 week treatment program Follow-up evaluations: Two weeks after receiving the last treatment, as well as one year following the last treatment session.	31: 8 male and 23 female participants. Group A : 16 Group B : 15 Gender ratios were not specified for the groups.	No mention made of assessor nor therapist blinding. 30/31 participants were naïve to osteopathy prior to this trial.	Randomisation via random permutations with MATLAB version 9.1		7	94%
2. Abdominal Pain: VAS					Placebo: Sham treatment (superficial abdominal massage only) versus Osteopathy treatment	This is a cross-over trial consisting of two consecutive 4 week long phases. <i>Phase I</i> (between EV1 and EV2): Group A received placebo Group B received osteopathy <i>Phase II</i> (between EV2 and EV3): Cross-over phase where groups switched interventions.		
3. Colonic Transit Time								
4. Rectal Sensitivity								
5. Evaluation to determine the absence / presence of depression.								
6. Dominant symptoms: Standardised FGID Questionnaire.								

<p>LIMITATIONS:</p>	<p>One strength of this study was that the criteria for the inclusion of participants were well defined; with the diagnosis of Irritable Bowel Syndrome being in accordance with the Rome III criteria. Only <i>refractory</i> IBS patients were included, signalling their dissatisfaction with drug therapies that they had followed without amelioration of their symptoms. The absence of concomitant organic disease had to be confirmed by endoscopic, laboratory, physiological as well as physical examination. This allowed for greater homogeneity of the groups under study, but limits the ability of the study to be extrapolated to IBS patients generically or with other permutations that are not listed as part of the Rome III criteria. This is further compounded by the fact that patients who are refractory to / dissatisfied with drug therapies, may have a different perception of the manual therapies that were utilised in this study. This is supported by the fact that the majority of the patients were female, who are more likely to be in favour of complementary alternative therapies anyway, which means that they are likely to come into the study with a positive attitude already (Van Tilburg 2008). This is particularly true if the male / female ratios between the groups were dissimilar (this is however not commented on in the report). The use of subjective outcomes tools may have been influenced by gender perception. This is however limited in that the subjective outcomes only account for three of the six outcome measures (symptom diary, pain recordings and FGID questionnaire). The generalisability of this study is further compounded by the relatively small sample size of 31 patients which could undervalue the significance of the results, particularly as the results would have required the use of non-parametric statistics.</p> <p>Routine treatment was permitted throughout the duration of the trial, which included a variety of osteopathic techniques that were specifically tailored to the “patient’s complaints”. This results in an inherent difference in the application of the osteopathic techniques per patient, decreasing the likelihood of a standardised approach. Therefore, this would weaken any conclusions that would suggest that “a standard osteopathic treatment is better than placebo”, as the techniques were individualised to the patients, making this study a comparison of case studies collected under a structured format of a randomised trial. Thus even though the same practitioner applied the intervention for all patients, the lack of similarity would be a limitation. This limitation is further compounded by the lack of difference that may be perceived between touch therapy / therapeutic touch and manual</p>
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	<p>therapies such as osteopathy. Patients were made aware that they would be receiving two different interventions. This means that some patients would have been able to identify the placebo treatment. This was in part countered by the fact that the majority of patients were naïve to osteopathic care (i.e. never having been treated before). The study, to its credit reported that some participants actually preferred the gentler placebo technique. This preference may indicate that the perception of the patients (regarding manual therapies) was a positive influencing factor and that touch therapy played a role in the outcome of this trial (Hussain and Quigley 2006). This would have had the potential to limit the difference between the groups in terms of the EV1-EV2 versus the EV2-EV3 outcomes, but would not have affected the overall 12 month follow up.</p> <p>The crossover design was selected to ensure that all participants received osteopathic treatment; and to minimise the effect of the variety of symptoms IBS patients may present with. But without knowing the short term and longer term effects of the intervention utilised, the impact of the osteopathy treatment on the subsequent placebo group would make it difficult to compare the second arm effects of the intervention versus the placebo.</p>
OUTCOME:	<p>The study reports that visceral osteopathy is effective in the short as well as long term in the amelioration of diarrhoea, abdominal pain and distension. Rectal sensitivity was also significantly reduced by visceral osteopathy, in contrast with the placebo treatment which did not produce the same results. These improvements were not emulated in colonic transit times. No significant changes were reported for constipation, nor for depressive symptoms, following either placebo or osteopathic treatment.</p> <p>It is interesting to note that the changes were reported both in the short term comparing EV1-EV2 to EV2-EV3 as well as the long term; as the long term changes cannot be compared between the placebo and the intervention groups as both the groups received osteopathic treatment.</p>

DISCUSSION:	<p>Patients with <i>refractory</i> IBS were evaluated during this trial, all of whom having failed to improve after a selection of drug therapies, and still sought high levels of healthcare, regardless of the aggressive pharmaceutical approach to the disease.</p> <p>Placebo effect may be amplified in these cases (greater female patient numbers, increased tendency for females to seek CAM care / manual therapy / touch therapy (van Tilburg <i>et al.</i> 2008) and the fact that a greater number of patients seemed to prefer the placebo, was not accounted for in this trial. Therefore a future study needs to consider careful stratification of age, gender, naivety, improving the blinding in the study and increasing the numbers of participants.</p> <p>Thus, the assertion that this study indicates that the osteopathic treatment is better than placebo, needs to be accepted with a degree of caution, based on the rigour of the inclusion criteria, the appropriateness of the study design to the conclusion drawn, particularly over the long term as well as the appropriateness of the assessment tools, when it would seem that the objective measures seemed to show less improvement over time as opposed to the subjective measures. Some of the outcomes of the measures may not have been appropriate for this group of patients.</p>
CONCLUSION	<p>Given the reviewers evaluation of the study with a 7/11, it shows that the rigour of the study was well thought out and structured in order to achieve the results obtained. However with the qualitative evaluation of the study, there are some significant factors that could have influenced the outcome of the study and therefore it is suggested that the study only provides at best moderate evidence to show that osteopathic treatment is better than placebo.</p>

Table 4.4 Tabulated feedback data of Article 2: PEDRO Scale						
AUTHOR(S):	Brice C. and Mountford R.					
YEAR:	2000					
TITLE:	A study into the efficacy of osteopathic treatment of irritable bowel syndrome					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	No	No	No	No	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	No	Yes	Yes	66%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	6/11	5/11	6/11	6/11	
		OVERALL PERCENTAGE AGREEMENT:				97%

Table 4.5 Analysis of Article 2								
AUTHOR(S):	Brice C; Mountford R.							
YEAR:	2000							
TITLE:	A study into the efficacy of osteopathic treatment of irritable bowel syndrome							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement
Symptom Diary: -Measures IBS related symptoms derived from the Rome criteria: Pain, Bloating, Frequency, Consistency and Nausea. Overall Well-being: -Visual Analogue Metric applied to monitor overall improvement of symptoms.	1. Baseline measures taken upon inclusion of the study. 2. Measures next recorded after 6 weeks of intervention. 3. Final measurements taken 3 months after the last treatment session.	4.5 months:	40 participants:	No mention made of allocation blinding method applied. No blinding of subjects or practitioners. Data was collected by nursing or administrative staff at the hospital.	Pseudo-random allocation: First 20 volunteers to the osteopathic group, second 20 to the allopathic group		6	97%
		Osteopathic group received four treatments over a six week period Allopathic group followed an individualised drug therapy regime for the six weeks. Follow-up assessment done three months after the last treatment.	20 allocated to receive osteopathic treatment while the other 20 participants received orthodox drug therapy. Gender ratios were not disclosed, it was merely mentioned that age and sex were comparable at baseline.		Allopathic group: 20 participants received orthodox pharmaceutical care, under the guidance of a gastroenterological consultant, for the trial period of six weeks.	Osteopathic group: 20 participants received four osteopathic treatments, applied by the same osteopathic practitioner, over the six week-long trial period.		

<p>LIMITATIONS:</p>	<p>The diagnosis of IBS was in accordance with the Rome III and Manning criteria. Participants needed to have suffered symptoms for at least six months to be eligible for the study. There was no upper limit to the condition duration that the patient had, the study does not suggest the exclusion of pathologies mimicking IBS and it is unclear whether the patients were screened for entry by one clinician (by inference that there were two persons treating the patients, it is implied that these two persons were also responsible for screening the patients). An age range of 20 to 80 years was set to limit medicinal treatment to patients below age 20 or over 80 years of age. In addition patients older than 80 years of age are not recommended to undergo routine osteopathic treatment, due to the high prevalence of contraindications in a degenerated skeletal system. This wide age range and thus the resultant possibility that patients may not have been homogenous between the groups in terms of the duration of the presenting complaint (IBS). This lack of homogeneity, it could be argued, is mitigated against by the baseline average in years with one group noting 41.9 and the other 45.5 years of age; however the age is not an indicator of when the IBS complaint actually started. Thus there may still be variance between the groups in terms of duration of the IBS.</p> <p>The above is compounded by the small sample size, as this may undervalue the clinical significance of the results achieved in this study. The study indicated that their time constraints dictated that only two groups of 20 participants could be included. pseudo-random allocation was implemented to generate the two sample groups. The first 20 participants who joined the trial were all allocated to the osteopathic group, with the following 20 to the allopathic group. Although not a bona fide method of randomisation, the authors deemed it fair enough as the random influx of patients at the clinic would lead to random allocation. This method of randomisation could however have allowed one or the other of the groups to be influenced by seasonal food and / or mood / affective changes affecting the IBS of the patients. The effects of these influencers on the outcome of the study are reinforced by the duration of the data collection period of 18 months.</p> <p>With regards to the treatment of the patients within the two groups. The allopathic interventions included a varied treatment</p>
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protocol in that patients were given either bulking agents, antispasmodics and / or tricyclic antidepressants. Thus “standard” treatment protocol indicated that the patients in this group varied according to the allopathic treatment each patient received. Therefore, the cumulative outcomes for the group, represents an outcome in terms of the pragmatic approach to allopathic treatment of IBS and not a clinical “gold standard” allopathic treatment approach. This is also true of the osteopathic treatment detailed in the study where the patients received a varied personalised combination of a number of interventions (again indicating the measurement of a pragmatic approach, as compared to a standardised osteopathic treatment approach). Thus the outcome of this research cannot be generalised to indicate that a specific intervention has a specific outcome on a specific IBS presentation. As a result replicating this study as part of future research OR in clinical practice is highly improbable and thus little benefit is derived from this study in terms of field practitioners being able to employ specific interventions for the best interests of their patients. .

To compound the above outcomes, the two groups received treatment interventions that have vastly different treatment action / mechanisms (hence the reason the study was limited to subjective outcome measures). The use of these self-administered subjective measures (to monitor any changes in symptoms and/or feeling of well-being), have inherent limitations themselves. However, the nature of the functional GI disorders restricts evaluation to such measures. Some scores (e.g. for consistency), could be confusing as they are compared to what the individual perceives as their norm. The significance of these scores remains uncertain, however the literature does argue that the influence of factors such as the “observer effect” and “Hawthorne effect” (McCambridge 2013), have a greater likelihood of being influenced by the patient’s subjective experience (potentially not measuring the reality of the IBS accurately) and thus impact on the outcomes achieved by the study (Mouton 1996). The above may further have been compounded by the fact that the study was conducted in a hospital setting. This setting has associated prior expectations – particularly the use of medication as the principle intervention. By contrast, osteopathic interventions do not provide the medications (as per the study intervention outline provided). This may influence the degree to which patients’ expectations are met and therefore their reporting of their subjective changes.

	<p>It is further noted that the study is limited in terms of its generalisability to males as only one male took part in the study. This will hamper the ability to accurately extrapolate results to the male population with IBS.</p> <p>The study does not specify the following, which would have improved the study and not further have complicated the limitations:</p> <ul style="list-style-type: none"> - Consistency in training of the persons screening the patients for inclusion. - Consistency of the persons measuring the outcomes (two persons noted). - Lack of objective outcome measures. - The study does not provide any indication of drops out due to the exclusion criteria and / or as a result of patient non-response, inability to complete the study or withdrawal for any other reason. No presented data shows that all 40 participants were included in the analysis as a result of the completion of the study. On the positive side and if all participants completed, then this study one of very few studies that actually attain more than 36 participants, which means that although statistically weak, this study is one of the strongest presented in this domain / field of study. - The location of the study implies that all patients were linked to prior treatment in the hospital setting. It is unclear whether patients were included that were not already prior patients at the hospital. This patient profile suggests that the patients in the study may have been longer standing chronic IBS patients and / or patients that had other co-morbid conditions, possibility complicating the treatment designed specifically for IBS. In addition, hospital patients may also represent those that are recalcitrant to specific forms of care and / or require long term monitoring to monitor response to medication (this may also have made them more responsive to alternative care options as represented by osteopathy in this study). This may underscore the reason why the study was structured as a pragmatic study and not a more rigorous clinical trial.
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OUTCOME:	<p>Notwithstanding the limitations outlined above, the results of this trial revealed that osteopathy was effectual in the short and longer term management of IBS. In the context of this pragmatic study, the outcomes suggest that osteopathic treatment was superior to orthodox pharmaceutical care in its efficacy in the amelioration of symptoms. This is reflected in that the outcome at six weeks of treatment showed that 95% of the osteopathic group reported a reduction in symptoms compared to 50% of the allopathic group. Another assessment was done three months after the last treatment, where 80% of the osteopathic group reported a long term reduction in symptoms versus 40% of the allopathic group.</p>
DISCUSSION:	<p>Despite the aforementioned limitations of this trial, the results produced in this study are clinically significant. On this basis it could be reasonably inferred that osteopathic treatment may provide greater relief compared to allopathic treatment in a hospital setting, with patients whose characteristics are similar to hospital based out-patients. This however needs to be contextualised in the limitations of this pragmatic randomised controlled clinical trial, which suggest that the outcomes need to be limited to patients of a similar nature to those reflected in this study and that the benefit accrued to patients that are dissimilar to this study are at best the same as conventional allopathic treatment.</p> <p>Conservatively, practitioners could therefore possibly advocate the use of osteopathy, only as an adjunct to and in cases similar to this study, as an <i>alternative</i> treatment modality. The need for further research, addressing the limitations of this study, is indicated to affirm the outcome of this trial, with more objective and structured outcome measures. Furthermore the cost effectiveness of the different treatment protocols should be investigated in order to determine their actual impact to improved health care delivery and effect.</p>
CONCLUSION:	<p>This study as indicated by Table 4.5 is of limited rigour attaining only 6/11 by the reviewers, along with the qualitative limitations, provides a study that is of limited evidence in support of osteopathic treatment being clinically superior to conventional medicinal care.</p>

Table 4.6	Tabulated feedback data of Article 3: PEDRO Scale					
AUTHOR(S):	Florance B.M; Frin G; Dainese R; Nebot-Vivinus M.H; Barjoan E.M; Marjoux S; Laurens J.P; Payrouse J.L; Hebuterne X; Piche T.					
YEAR:	2012					
TITLE:	Osteopathy improves the severity of irritable bowel syndrome: a pilot randomised sham-controlled study					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	Yes	No	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	Yes	No	66%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	7/11	9/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				94%

Table 4.7 Analysis of Article 3

AUTHOR(S):	Florance B.M; Frin G; Dainese R; Nebot-Vivinus M.H; Barjoan E.M; Marjoux S; Laurens J.P; Payrouse J.L; HebutterneX;Piche T.							
YEAR:	2012							
TITLE:	Osteopathy improves the severity of irritable bowel syndrome: a pilot randomised sham-controlled study							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement
1. Stool Diary: Describes stool frequency and form. 2. Level of Satisfaction 3. French validated IBS-severity scoring system. 4. Quality of Life: a) FIS b) BDI c) HAD	1. Stool Diary: recorded for 10 days before start of intervention as well as 10 days leading up to the final day, Day 28. 2. Level of satisfaction recorded at the end of the trial. 3. The questionnaires were completed once on the first day of the trial, prior to applying treatment; once on Day 7 of the trial; and finally on the last day i.e. Day 28.	Five and a half weeks (38 days)	30 participants; 23 female to 7 male ratio. 20 allocated to intervention group: 15 F, 5 M. 10 allocated to sham- control group: 8 F, 2 M.	Self-administered subjective measured employed to evaluate participants progress. Practitioner was unaware of the IBS subtype that the participant belonged to, and was not involved in data analysis	Randomization was not clearly described. Mention was only made of an unequal 2:1 allocation.		7	94%
		Treatment received on the first day (10); once more a week later Day 7 (17); and final measurement session on Day 28 (38), i.e. 4 weeks after the start of the trial.			10 participants in Sham Osteopathy Group: Gentle massage applied to the spine as well as the abdomen	20 participants in Intervention Group: Standardised osteopathic treatment comprised of spinal as well as visceral manipulation using direct as well as indirect techniques.		

<p>LIMITATIONS:</p>	<p>The inclusion and exclusion criteria were extensive and well defined for this study, with the Rome III criteria being requisite for the diagnosis of IBS. Participants needed to experience IBS related symptoms for more than 25% of the time. Although this represented an extensive inclusion criteria, the large variance in the duration of the condition, had the potential to increase the differences in terms of the effectiveness of the interventions. This may however have been limited by the inherent differences in symptoms experienced by patients whom suffered from IBS-M (mixed with both constipation and diarrhoea), who were not included in this study. In addition, this study, utilised investigations to limit other mimicking pathologies (e.g. celiac disease, inflammatory bowel disease, lactose intolerance, rheumatologic disease, severe depression and anxiety as well as renal and thyroid dysfunction).</p> <p>Further positives in the study methodology included that dietary customs were unchanged for three months leading up to the trial and for the duration thereof. The use of anti-depressants, anti-inflammatory drugs and / or analgesic medication was eliminated and alcohol / tobacco use was discouraged and patients excluded if they consumed these. Patients were required to remain on their IBS medications (anti-spasmodics, anti-diarrheal or laxatives), however the comparability of the groups in terms of these medications were not included. Therefore the homogeneity of the groups in this respect is unknown and its effect on the outcome is limited. Optimal blinding was ensured by excluding any patients who were familiar with or had previously had received osteopathic treatment. This blinding also ensured that the patients were unable to identify the sham treatment included in the study.</p> <p>With regards to the limitations, the sample size of 30 is very small (particularly as the groups were not equally matched in size). This may devalue findings on bowel habits combined with the lack of IBS duration homogeneity and the lack of power based on the sample size limits the ability of the study to generalise the findings of the study. This is further compounded by the chosen patient-allocation method used [i.e. unequal 2:1 randomisation (viz. osteopathy:sham)], which does not effectively remove the researcher bias and inclusion bias of patients into each group. Based on the methods of allocation it is possible that patients</p>
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could have been “allocated” per group in order to favour one group over another. The patients were treated only twice in the 38 day duration of the study. The likelihood of finding improvement in the symptoms of the IBS in these presenting patients is therefore not high (as it seems that most patients were chronic sufferers). It would have been more effective to increase the number of treatments for patients with IBS of longer durations. The follow-up period of 13 days following completion of treatment, is relatively short. This limits this study to report on short-term effects of osteopathic treatment only.

Further limitations of the study included the following identified problems:

- A lack of control of the interpersonal interactions between practitioner and participant, which may account for the benefits of osteopathy over the sham protocol.
- Although patients were naive to osteopathic treatment, it is unclear as to whether the patients were blinded to the sham and osteopathic intervention treatments in the study.
- The study indicated that the person treating the patients was blinded to their type of IBS, however it is unclear from the study, as to whether the person(s) treating the patients were blinded to the interventions that they delivered (i.e. who was seeing which patients).
- Although there was a similarity between the modalities utilised and this may have “fooled” the patient, it is possible-based on the theories of therapeutic touch (Pitz *et al.* 2005) that they both enabled the same mechanisms (therefore the sham was not actually a sham, but rather an active treatment modality).
- The treatments utilised in this study were both protocols, therefore it is not possible to indicate a specific part of the protocol as being the active intervention.
- The gender distribution of study participants (viz. female predominance of 23:7 ratio) is not representative of the population at large, which may hamper the ability to extrapolate findings to the general population of IBS cases.

Collectively, the small sample, low to medium severity of the IBS and the fact that the patients were allowed to continue on medication, indicates that there may be a masking of the actual treatment effect of the interventions in this study. These effects

	include the possibility of the patient outcomes hitting the “floor” or reaching the “ceiling effect” (Bruce <i>et al.</i> 2013).
OUTCOME:	Both groups reported a decrease in symptom severity by days 7 and 28. The decrease was significantly more marked in the osteopathic group by day 7 (after the second and final osteopathic treatment); however, by day 28 the difference was no longer significant. Although both anxiety and depression scores decreased, there was no significant difference in groups. Neither stool frequency nor stool consistency was significantly altered during the study period.
DISCUSSION:	From the outcomes achieved in this study, it would seem that there was no difference between the two groups in the medium term (short lived differences existed at the 7 day period only). The lack of differences between the groups could be attributed to the multiple limitations that are noted in the limitations above. Therefore the outcomes of this study would need to be confirmed by a follow on study which simultaneously addresses the methodological flaws that are presented in this study.
CONCLUSION:	Given that the reviewers rated this article highly (7/11), it indicates that the study had moderate to high levels of rigour in its methodological design. However when reviewing the article from a qualitative perspective, there were some inherent limitations which had the propensity for affecting the outcomes of this study. As a result, this study only provides moderate levels of evidence in support of the outcomes, which showed limited differences between the groups in the medium and longer term. These results however may have been different if the flaws in the study had been addressed and future research addressing these flaws may provide a basis for a more solid conclusion to the study.

Table 4.8	Tabulated feedback data of Article 4: PEDRO Scale					
AUTHOR(S) :	Gamber R.G; Shores J.H; Russo D.P; Jimenez C; Rubin B.R.					
YEAR:	2002					
TITLE:	Osteopathic manipulative treatment in conjunction with medication relieves pain associated with fibromyalgia syndrome: Results of a randomised clinical pilot project					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	Yes	Yes	No	Yes	66%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	No	No	No	66%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	Yes	No	Yes	Yes	66%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	No	No	No	No	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	No	Yes	Yes	66%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	No	Yes	66%
11	The study provides both point measures and measures of variability for at least one key outcome	No	No	No	No	100%
	TOTAL SCORE	7/11	4/11	4/11	6/11	
		OVERALL PERCENTAGE AGREEMENT:				85%

Table 4.9 Analysis of Article 4

Table 10: Analysis of Article 1								
AUTHOR(S):	Gamber R.G; Shores J.H; Russo D.P; Jimenez C; Rubin B.R.							
YEAR:	2002							
TITLE:	Osteopathic manipulative treatment in conjunction with medication relieves pain associated with fibromyalgia syndrome: Results of a randomised clinical pilot project							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	TotalPercentage Agreement
1. Pain Perceptions: Pain thresholds 2. Chronic Pain Experience Inventory 3. Present Pain Intensity Rating Scale 4. Self-Evaluation-Questionnaire: Relating to participant's response to treatment. 5. Activity of Daily Living: Stanford Arthritis Centre Disability and Discomfort Scales: Health Assessment Questionnaire. 6. Depression: Centre of Epidemiological Studies Scale	Repeated-measures were assessed at the following points: Weeks: one; two; four; seven; 11; 15; 19 and 23	Six months	24 female participants were included and allocated to one of four different treatment groups. Thereby creating four sample groups of six participants each.	Allocation was via sealed envelopes containing pre-coded cards specifying one of the four treatment groups. A research <i>technician</i> was responsible patient screening. A research <i>coordinator</i> evaluated medical reports to approve eligibility of the candidates. Clinical assessments were performed by a qualified research <i>nurse-specialist</i> unaware of which treatment group the participant belonged to. One osteopathic <i>practitioner</i> applied all the manipulations.	Pre-coded cards in sealed envelopes were used to allocate participants to one of four treatment groups. <			

<p>LIMITATIONS:</p>	<p>This study pertains to fibromyalgia, and does not directly address IBS. It was nonetheless recommended for inclusion into this systematic review by participating by the participating reviewers. The recommendation was based on the fact that fibromyalgia is described as a functional somatic syndrome, as is IBS, and is prevalent in up to 50% of IBS patients (WGO 2015; North <i>et al.</i> 2007; Whitehead <i>et al.</i> 2002; Sperber <i>et al.</i> 1999). Some clinicians believe that these conditions are indivisible and should rather be grouped together under the single “umbrella” term of <i>functional somatic syndromes</i> (FSS) (Heningsen <i>et al.</i> 2007).</p> <p>An appointed research technician screened all patients at the Rheumatology Clinic at the University of North Texas Health Science Centre. The screening of patients substantially increased the rigour of the study. Inclusion criteria included the following: diagnosis of Fibromyalgia (FM) in accordance with the 1990 American College of Rheumatology criteria for FM; no concomitant illnesses (including peptic ulcer disease, cardiac arrhythmias or disease that require Central Nervous System suppression); age between 30 and 65 years of age; no other participation in any physical or manual therapies including massage, chiropractic, physiotherapy or OMT for the duration of the trial. This was further enhanced by the use of a research coordinator who then assessed the medical records to confirm subject eligibility for inclusion into the study.</p> <p>The study was weakened by the small sample size of twenty-four participants. The participants were allowed to continue with their current medication which they received for free (for a six month period) in addition to the receipt of \$100 for travel and expenses in participating in the study. These latter two issues confound the study in that the participants may only have volunteered to participate in the study based on these incentives and may also have felt that they would need to report improvement during the course of the study. Both of these factors had the ability to confound and affect the outcomes of the study, which with the small sample size means that the outcomes may represent improvement beyond the clinical reality.</p> <p>With regards to treatment and interventions, it was clear that the osteopathic practitioner provided the OMT and that one other physician oversaw the medication use for the duration of the study; it was however unclear as to who applied any auxiliary therapies (e.g. heat). In terms of the understood interactions, it seems that 50% of the patients were exposed to the osteopathic</p>
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practitioner and 100% were exposed to the other physician. The inequality in the exposure to those physicians providing or monitoring patients may have had an effect on the outcomes of the study a.k.a. “Observer effect” and the “Hawthorne Effect” (McCambridge *et al.* 2013). This inequality is further enhanced in that the treatment protocols provided for each of the patients was individualised per patient (type of intervention and the sequence of intervention), thus making the small groups of six patients potentially less homogenous and more like a case series set. A more standardised treatment protocol would have been more appropriate in a research setting, such that the protocol was tested. In the current context there is limited ability of the outcomes of this study to support any individual intervention or protocol.

The manner in which the research is presented, it is possible to identify the nurse specialist as a blinded observer, but it is unclear whether the person who applied the intervention/ OMT specialist / physician monitoring patient medication were also the research technician or research co-ordinator OR whether these positions were filled by the physicians that are regulating the medication use. Thus, it is not possible to fully understand whether the study was fully blinded in terms of the inclusion or patients and subsequent measurements.

All measurements were subjective in nature and therefore it is possible that prior exposure to one or more of the treatment interventions could have influenced the outcome of the study. Therefore, patient naivety should perhaps have been considered a factor in this study, given the small sample size and the subjective nature of the outcomes. These would have assisted in negating the effects of the “Observer effect” and the “Hawthorne Effect” (McCambridge *et al.* 2013)

Lastly, the current study can only be generalised to female patients, as no males were included in the study.

OUTCOME:	<p>The authors of this study indicate that the interventions produced significant findings between the four different treatment protocol groups in terms of the following measures: pain threshold, pain perception, attitude toward treatment, activities of daily living and chronic pain traits.</p> <p>These results all proved in favour of the two OMT groups (groups 1 and 2) [participants in both manipulated groups] reporting significant improvement compared to those whom did not receive OMT. When reviewing the above measures individually, it is noted that not more than 50% of the measured outcomes actually presented with significant findings (e.g. pain thresholds was only significantly improved for 3/20 tender points). Thus, it is not possible to state categorically that the findings of this study carry any significant clinical improvements for any of the measures between the groups. Therefore, the summary provided by the authors indicating that this study revealed OMT in combination with medical care to be more effective than medical care alone; needs to be read with caution in that the outcomes are limited to a small percentage within a small group of patients.</p>
DISCUSSION:	<p>It would seem that the small sample size, the case series like application of the intervention and the limited outcomes based on objective measures are the main hindrances in this particular study. These limitations make it particularly difficult to accept the noted outcomes provided by the authors, indicating that the two OMT groups (groups 1 and 2) fared better than the heat group and the control group. It may be more realistic to have another study completed within the methodological framework presented with the flaws addressed and the sample size increased in order to verify these results and have them be applied in clinical practice.</p>
CONCLUSION:	<p>With the qualitative review of the article it can be seen that there are several limitations that affect the outcomes obtained in the study. These limitations are also reflected in the reviewer's conclusions noted in Table 4.8, where an allocated score of 6 seemed to indicate consensus among the reviewers. This is an average score indicating that there is a lack of methodological rigour in this study and limited contribution to the evidence in support of the intervention. Therefore, at very best, this study provides a basis for verification of their results in a similar such study addressing the flaws and that no firm conclusions can be drawn from the outcome obtained.</p>

Table 4.10	Tabulated feedback data of Article 5: PEDRO Scale					
AUTHOR(S):	Hundscheid H.W.C; Pepels M.J.A.E; Engels L.G.J.B; Loffeld R.J.L.F.					
YEAR:	2006					
TITLE:	Treatment of irritable bowel syndrome with osteopathy: Results of a randomized controlled pilot study					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	Yes	Yes	No	Yes	66%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	No	Yes	Yes	66%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	No	No	No	No	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	6/11	6/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				94%

Table 4.11 Analysis of Article 5

AUTHOR(S):	Hundscheid H.W.C; Pepels M.J.A.E; Engels L.G.J.B; Loffeld R.J.L.F.								
YEAR:	2006								
TITLE:	Treatment of irritable bowel syndrome with osteopathy: Results of a randomized controlled pilot study								
STUDY PROPERTIES:									
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement	
1. Overall Changes 2. FBDSI Score 3. Symptom Score 4. Quality of Life	1. An overall perception of symptom changes was described at three intervals : one, three and six months follow ups . 2. FBDSI: at inclusion into the study as well as at 6 month follow up. 3. Symptom Score reported on at three intervals: at inclusion of the study, and again on three month and six month follow ups respectively. 4. Quality of Life: measured upon	A run-in period of two weeks preceded the randomisation of participants. Follow-ups were scheduled for one, three and finally six months after randomisation.	Initial sample size of 39 eligible candidates randomly assigned to one of two groups : 1. Osteopathy Group included 20 (6 M, 14 F), with one drop out (gender not stated), resulting in 19. 2. Standard Care Group included 19, with two drop outs (gender not stated),	Patient blinding is not possible where patients are familiar with the intervention. Validated subjective outcome measures were self-administered by the patients without any influence from the gastroenterologist or osteopath. Data analysis was performed by an investigator who had no knowledge of patient information. To minimise investigator bias, follow-up assessments were performed by an independent practitioner of the Department of	Randomisation by closed envelopes containing one of two allocated intervention groups. Standard Care Group: Regime involves the intake of fibre, laxatives and/or anti-diarrhoeal and anti-spasmodic medications Standard care describes the conventional approach to IBS, an accepted treatment protocol for this disorder. No expectations were placed on the osteopathic results, hence sham osteopathy could not		Osteopathic intervention applied via the “black box” method, using a patient-specific therapeutic approach, according to the practitioner’s own insights. Participants each received five treatments once every two to three weeks. Members of this group were instructed to refrain from the use of any	7	94%

	inclusion and again at each of the five treatment sessions.		<p>resulting in 17.</p> <p>Final sample size of 36.</p>	Gastroenterology.	be feasibly employed as a control.	medications, and did not increase their fibre intake		
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LIMITATIONS:	<p>Criteria for inclusion in this study were expansive and well defined. Candidates were eligible if they had been diagnosed, by a gastroenterologist, using the Rome II criteria for IBS, and experienced moderate abdominal complaints on at least three days in the week leading up to inclusion into the study. Exclusions were made based on other systemic diseases, prior abdominal surgery (apart from appendectomy, herniotomy, hysterectomy and haemorrhoid surgery), psychiatric illness and alcoholism. This improved the homogeneity in the sample, given the relatively small sample size.</p> <p>This study, attempted to improve both compliance and patient retention in the study, by employing Dutch questionnaires, however these self-administered questionnaires do have limitations as patients often report what they think the practitioner wishes to hear (Hawthorne Effect). Therefore the study could have been strengthened by the use of more objective outcome measures to allow for an analysis of the subjective measures that their congruency with the objective outcome measures. In addition, it is unclear as to whether these questionnaires were appropriately developed through an expert group and pilot testing. If the latter procedures were not completed (or referenced to a study), then it is unlikely to have had its concurrent validity measured, which then questions the actual ability of the questionnaires to measure the actual treatment outcomes accurately .</p> <p>The problem of recording the outcomes is compounded by the lack of a true control group. A standard care protocol that is conventionally utilised was followed, as it is considered an acceptable treatment for IBS (and fulfils the capacity of a control intervention).</p> <p>In addition to the above, the inherent differences in the osteopathic “black box” method contribute to this study’s limitations. The patient-specific approach and treatment regime is not ideal in a research setting as too many variables need to be considered (and the individual patients almost become case studies in their own right), and the uniformity of treatment application is not plausible (as different case series are clustered in the format of an RCT) . This approach is further compounded by the fact that the clinical decision making and implementation of “black box” care is largely depend on the expertise of the practitioner and may therefore not be reproducible in a follow on study or in clinical practice.</p>
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OUTCOME:	<p>Overall improvement was reported by all participants who received <i>osteopathic treatment</i>. Of these 68% reported definite improvement while 27% reported slight improvement. One participant was completely free of symptoms at the end of the trial.</p> <p>Of the <i>standard care group</i> only 18% of the participants reported definite improvement, while 59% showed slight improvement. Deterioration of the condition was reported in 17% of the participants who followed the standard drug regime. These results support the significance of osteopathy in the management of IBS.</p>
DISCUSSION:	<p>This clinical trial produced statistically significant results that support the use of osteopathic treatment in the management of IBS related symptoms. Inferential statistics provided allow for a valid conclusion to be drawn regarding osteopathic intervention alone as well as in comparison to the standard care regime. The follow-up in this trial was six months, as possible placebo effects were expected to have worn off during this period.</p>
CONCLUSION:	<p>Based on the results of this study, it can be reasonably inferred that osteopathic treatment may be a promising option for IBS sufferers. Statistical evidence provided not only implies that osteopathy is a successful therapeutic modality in the treatment of IBS, but also strongly suggests that it is more effective than the standard care protocol. Osteopathy may therefore be responsibly advocated, not only as an adjunct, but as a more effective alternative treatment option for IBS patients.</p> <p>These assertions, however, need to be taken in the context of the reviewers findings which suggest that this study (based on its limitations) may only provide a moderate level of evidence in support of osteopathic care (7/11) (Table 4.10) and that the results need to be read with caution until further studies provide supporting evidence for the outcomes of this particular study. The positive results do, however, highlight the need for further research to be conducted in this field, while addressing the limitations of this study, so to advance the evidence base for clinical practice.</p> <p>These assertions however need to be taken in the context of the reviewers findings which suggest that this study (based on its limitations) may only provide a moderate level of evidence in support of osteopathic care (7/11) (Table 4.10) and that the results need to be read with caution until further studies provide supporting evidence for the outcomes of this particular study.</p>

Table 4.12 Tabulated feedback data of Article 6: PEDRO Scale						
AUTHOR(S):	Kuttner L; Chambers C.T; Hardial J; Israel D.M; Jacobson K; Evans K.					
YEAR:	2006					
TITLE:	A randomised trial of yoga adolescents with irritable bowel syndrome					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	Yes	No	No	No	66%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	8/11	7/11	7/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				97%

Table 4.13 Analysis of RCT Article 6

AUTHOR(S):	Kuttner L; Chambers C.T; Hardial J; Israel D.M; Jacobson K; Evans K.							
YEAR:	2006							
TITLE:	A randomised trial of yoga adolescents with irritable bowel syndrome							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 13	Total Percentage Agreement
1. Pain Intensity: NMS 2. Pain Coping Questionnaire 3. GI Symptoms: Blanchard Checklist 4. Functional Disability Inventory 5. Revised Child Manifested Anxiety Scale 6. Children's Depression Inventory	Measures were taken once prior to any intervention, and again at the follow up 4 weeks later.	4 weeks	28 participants (20 female, 8 male)were recruited and randomly assigned to two groups of 14. Group A: Yoga group of 14 (12 female, 2 male). Group B: Waitlist Control group had 3 male drop-outs reducing the sample size to 11 (8 female, 3 male). Resultant number of participants : 25 (20 female, 5 male)	Self administered subjective measure questionnaires were used in this study. The intervention was applied by the participants themselves, within their home environment.	Randomisation by means of a sequence of randomly determined numbers Waiting List Control Group participants did not receive yoga instructions, instead continued with their usual management protocol for the duration of the study.		7	97%
						Participants assigned to the Yoga Group were given verbal instruction, live demonstration as well as assisted training from a yoga instructor. All participants were given the same yoga poses and breathing routines, which they were expected to perform once daily. The routine was chosen based on its effect on the abdomen and GIT.		

LIMITATIONS:	<p>In terms of this study, the following was noted:</p> <ul style="list-style-type: none"> • The candidates were telephonically screened to ascertain whether they met the Rome I criteria for IBS. The relatively small sample size of 28, was accepted by the authors as it is indicated that this sample size was calculated to be adequate for inter-group analysis, although it would have utilised non-parametric statistics which are not as strong as the parametric statistical analysis tests. • The control was not clearly enough defined, uncertainty prevails as to the difference in intervention protocols applied to the two Groups. Was the difference a matter of time delay? In that Group B “waits” for four weeks, during which they continue conventional treatment, while Group A received yoga intervention within the first four weeks. • The prescribed intervention is applied within the home environment of the participant. This may give rise to issues of non-compliance and/or incorrect practice. Although it is reported that participation was fairly frequent (mean 6.81 of 10), many of the participants described difficulties adhering to the treatment programme (over four weeks). Issues raised included time constraints in lieu of other commitments as well as the inability to practice yoga whilst in pain. However, all but one of the participants reported that they would continue to do yoga in a bid to manage their IBS, and that they found it enjoyable and easy to do. One of the factors influencing the participation was pain and it is noted that some participants suggested that the instructional video include a greater variety of poses so that they could select postures according to their levels of pain or discomfort. In terms of motivation, consistent application and participation, this study may have benefitted from a more structured, individualized or interactive approach (e.g. group classes may motivate individuals to practice yoga daily, at the same time ensuring that the most appropriate postures are held correctly)..
OUTCOME:	<p>Participants in the yoga group described lower anxiety and functional disability levels subsequent to intervention, compared to control group members. After combining pre- and post-intervention data for the two groups, it was found that gastrointestinal symptoms as well as “emotion-focussed avoidance” were both lessened by the practice of yoga. All but one participant stated that they planned to continue practicing yoga to manage their IBS related symptoms. It could therefore be reasonable inferred that yoga holds promise as a useful intervention for this population.</p>

DISCUSSION:	<p>Due to exploratory nature of this pilot study p values of 0.1 or less were adopted as worthy of interpretation by the authors. Functional disability ($p=0.073$); emotion-focused avoidance ($p=0.09$) and anxiety levels ($p=0.09$) were all key measures that showed significant improvement. This study provides statistically meaningful evidence to support the use of yoga in the management of IBS related symptoms, particularly anxiety, functional disability and avoidance behaviours. It could therefore be reasonable inferred that yoga holds promise as a useful intervention for this population.</p>
CONCLUSION:	<p>Pilot studies are inherently limited in their statistical power, however, the positive results achieved not only depicts yoga as a promising treatment option for adolescents suffering from IBS, but also provides rationale for conducting further clinical trials to substantiate the role of yoga in the management of IBS. This is substantiated by the high 7/11 rating provided by the reviewers for this particular study, indicating that the study has appropriate methodological rigour to underscore and support the outcomes and conclusion drawn by the authors; while it provides moderate support for the use of yoga as an intervention in the management of IBS related symptoms.</p>

Table 4.14	Tabulated feedback data of Article 7: PEDRO Scale					
AUTHOR(S) :	Lamas K; Lindholm L; Stenlund H; Engstrom B; Jacobsson C					
TITLE:	Effects of abdominal massage in management of constipation- A randomised controlled trial					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	7/11	7/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				100%

Table 4.15 Analysis of Article 7

AUTHOR(S):	Lamas K; Lindholm L; Stenlund H; Engstrom B; Jacobsson C							
YEAR:	2009							
TITLE:	Effects of abdominal massage in management of constipation- A randomised controlled trial							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement
1. GSRS: Abdominal Pain Reflux Indigestion Diarrhoea Constipation 2. Stool Diary reporting Monday-Friday on frequency, consistency, size, time it takes to defecate, intake of laxatives, fibre and fluids.	Three GSRS were recorded: 1. At baseline prior to intervention 2. At week four 3. At week eight A Stool Diary was also completed at the above mentioned intervals.	The trial was conducted over a nine week period: One week of baseline followed by eight weeks of treatment.	60 participants initially: Attrition of eight (four from intervention group; four from control group). Resultant sample size of 58 with a male to female ratio of 8:50. Intervention Group of 29 (3:26); Control Group of 29 (5:24).	Self-administered Subjective questionnaires were employed in this study. 96% of the massages were applied by the first author (Lamas)	Block randomisation was used to allocate participants to one of two groups:		7	100%
					Control Group participants received no massage, and were asked to continue using laxatives.	Intervention Group participants received a mean number of 32,14 (with a range of 22 – 39) 15 minute long (light pressure) abdominal massages.		

<p>LIMITATIONS:</p>	<p>Inclusion criteria were well defined by the authors, with participants screened to meet Rome II criteria for functional constipation. It must be emphasised that the inclusion of this study (which is not directly related to IBS), is based on the common diagnostic criteria, as well as the fact that a high prevalence of this condition is observed in IBS patients (Quigley <i>et al.</i> 2015). As before mentioned in section 2.2.5, clinicians are faced with a clinical conundrum in distinguishing between the two disorders as the symptoms are so similar, while the viability of the existing “artificial division” between these two FGIDs is disputed (Suares and Ford 2009).</p> <p>Inclusion required participants to utilise medication based treatments for the condition for the duration of the study (control group was laxative use only compared to the laxative and intervention group). It was not noted that the participants were naive to the intervention options and were recruited on a volunteer basis, raising concern as to possible bias towards (positive or negative) massage. This may have meant that patients elected to participate in order to receive an alternative form of treatment or that the patients opted for the medication only group as they felt that massage would not work. With naivety to the intervention forms and / or a perception question indicating the patients knowledge and expectation of the interventions, makes it difficult to ascertain whether improvement was due to anticipation / expectation and / or lack of blinding (Mouton 1999).</p> <p>The period of the study (eight weeks) could have influenced the measurements obtained as it is indicated that there were only three time points at which measurements were recorded (baseline, week four and week eight). All the outcome measures were subjective and it is questioned as to whether the participants were able to supply accurate information reading change, as the three recording points would have required the participant to recall data for a period of one week, four weeks and the subsequent four weeks respectively. This makes the data subject to memory “decay” or recall bias (Mouton 1999). The study would also have been strengthened by at least one outcome measure that was objective in nature to ascertain whether the intervention affected the actual stool movement in the constipation, or merely addressed the psycho-emotional component of the condition.</p>
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	<p>From the results, the baseline readings suggest that the intervention group was more constipated than the control group, indicating that the intervention had a greater ability to improve than the control [i.e. the control group had a greater chance of “hitting the floor” (Bruce <i>et al.</i> 2013)] prior to the intervention group, making the increased improvement possible in the intervention group an artificial significant improvement.</p> <p>The consistency of use of the various medication based treatments was not reported in the study; therefore it is unclear if there were differences between the groups in terms of medication consumption for IBS. Thus, the use of the diary to report reduction in the use of laxatives as well as intake of fibre and fluid is problematic as it assumes that all patients could report on these findings (i.e. all on laxatives) and that there was no difference between the groups in terms of their usage of medication, bulking agents and other medicinal interventions at the start of the study. This further becomes problematic if these findings were utilised as a proxy marker for showing that massage has an effect.</p> <p>The above concerns are amplified, in that the Bowel Diary protocol (for unspecified reasons) did not extend itself to recording changes over the weekends. This further reduces the possibility to define differences between the groups, as well as underestimating the number of bowel movements recorded, effect of medication utilised on weekends and the effect of a non-normal (non-week day) routine over the weekends. This is seen in that the participants were not instructed to avoid other treatment options over weekends or outside of the Monday to Friday (5 day) periods during which the study officially required them to participate over the eight week period.</p> <p>In terms of treatment, the design including the duration of the massage (i.e. 15minutes), was based on findings from a pilot study conducted by the first author in 2006 (Lamas <i>et al.</i> 2006). Notwithstanding this, the positive effect of personal interaction between practitioner and participants has not been controlled for in this study; as the control group on medication did not have the same interactions as compared with the massage group. This may have unduly influenced the outcomes in terms of the documented effects of touch therapies (Hussain and Quigley 2006; Pitz <i>et al.</i> 2005).</p>
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	<p>Several practitioners administering treatment, although training was provided, has the ability to result in different treatment styles, different practitioner and patient interactions and therefore variable clinical outcomes. It is therefore questionable why a small percentage patients (4%) was treated by these additional therapists.</p> <p>Patient improvements were only recorded on subjective outcome measures, compounded by the fact that patients were able to be treated at the clinic versus at home, either detracting from or enhancing a clinical outcome artificially when only subjective measures are utilised in providing feedback. Of the 60 participants that were included 15 received treatment at home to improve compliance. The impact of the surroundings, increased comfort as well as the lack of having to accommodate the research within their schedules may have made these 15 patients report increased subjective improvement. This may have affected the outcomes per group as all of these 15 were in the intervention group.</p> <p>Since male participation was limited (8 of 58), this raises concerns that the results of this trial may not be accurately representative of the general population, at the same time, it must be mentioned that IBS is in general more prevalent among the female population (Lovell and Ford 2012 b).</p> <p>On a positive note, the study did report that there were drop outs in the study and that they utilised intention to treat analysis for three patients in each of the two groups. This outcome does not adversely affect the study as equal numbers (1 in each group dropped out) and the majority (in excess of 80%) completed all measurement time points.</p>
OUTCOME:	<p>From the results, and according to the discussion provided by the authors, no significant differences were found between the two groups after four weeks of treatment. The intervention group had significantly less severe GI symptoms following eight weeks of treatment. Bowel function increased after the first month of receiving treatment, however, at eight weeks following commencement of treatment, pre-treatment levels of dysfunction were once again reached (regression to baseline). Stool size and consistency was not influenced by abdominal massage, while participants reported an increase in frequency of</p>

	<p>defecation. An interaction was noticed between the baseline values of GSRS total scores and massage, the more severe the baseline symptoms, the greater the impact of massage at week eight. This seems to indicate that massage may prove to have better effect on sequential symptoms, rather than on constipation itself.</p>
DISCUSSION:	<p>No immediate effects were noted following massage, results were monitored over a four and then eight week period, during which five massages were administered each week. This protocol could prove very costly when treatment is sought from a practitioner. Demonstrating self-massage techniques to patients may be a more cost-effective.</p> <p>This study adequately demonstrates the efficacy of abdominal massage in the management of IBS related symptoms. After eight weeks of receiving abdominal massage, the intervention group displayed statistically significant changes in bowel function and symptoms compared to the control group.</p>
CONCLUSION:	<p>This study investigated the efficacy of abdominal massage in the management of chronic constipation. Significant changes were detected in the massage group compared to the control group. After eight weeks of massage, participants reported an amelioration of GI symptoms associated with constipation and abdominal pain syndrome, as well as an increase in frequency of bowel movements. However, massage therapy did not result in a decrease in laxative consumption. It can therefore only be considered a possible adjunct rather than an alternative to laxative therapy. Because changes in measures were evident only after eight weeks of treatment, it can be reasonably inferred that massage be a long-term form of treatment.</p> <p>Although the reviewers rated the rigour of this study highly (7/11 with 100% agreement amongst the reviewers) and the study indicated that massage had a positive effect on constipation, the medication use in the participants did not change over the period of the study. Therefore this study provides moderate evidence in support of massage as an adjunctive therapy as opposed to a principle therapy in the treatment of chronic constipation.</p>

Table 4.16	Tabulated feedback data of Article 8: PEDRO Scale					
AUTHOR(S):	Munton R.					
YEAR:	1999					
TITLE:	The efficacy of spinal manipulation in the management of irritable bowel syndrome					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	Yes	Yes	Yes	Yes	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	Yes	Yes	Yes	Yes	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	9/11	9/11	9/11	9/11	
		OVERALL PERCENTAGE AGREEMENT:				100%

Table 4.17 Analysis of Article 8

AUTHOR(S):	Munton R.							
YEAR:	1999							
TITLE:	The efficacy of spinal manipulation in the management of irritable bowel syndrome							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Rank out of 11	Total Percentage Agreement
1. Short-Form McGill Pain Questionnaire (SF-MPQ): -Measured abdominal pain intensity levels. 2. Accompanying Symptom Questionnaire (ASQ): -Monitored participants' bowel symptoms over the course of the study period. 3. Life Line Stress Questionnaire (LLSQ): -Monitored stress levels during the course of the study.	The self-administered subjective questionnaires were all completed prior to treatment on the first and seventh visits, and again on the final follow-up assessment visit one month following the last treatment session.	Eight weeks: Four weeks treatment period, with an additional one month follow-up period.	Thirty-four participants were initially recruited, four of whom could not complete the trial, three due to work and travel commitments and one participant was not comfortable being manipulated. The resultant sample size: Thirty participants were randomly allocated to one of two groups: Fifteen to the intervention (SMT) group (and fifteen to the control (placebo) Group. .	A single blinded study: Participants were uninformed as to which group they had been allocated to. -As a result of subject blinding, assessor blinding is applicable to this study.	Pieces of paper with numbers 1-30 picked from an envelope. Even no's: intervention; Odd no's: control. Control group: Participants treated with an inactive ultrasound machine over fixated spinal segments The same time and level of enthusiasm applied to the intervention group was dedicated to the control group.	Intervention group: Received spinal manipulative therapy, customised according to findings on palpatory and orthopaedic examination: Two sessions weekly for three weeks and one more in the fourth week.	9	100%

<p>LIMITATIONS:</p>	<p>The criteria for <i>inclusion</i> to or <i>exclusion</i> from this study are well defined by the author :</p> <p>The inclusion criteria required that the patients be between the ages of 18 to 50 years, that they must have suffered from at least three of the six symptoms that comprise the Manning Criteria for diagnosis of IBS. In addition the patient was required to present with one of the following , as determined by spinal examination:</p> <ul style="list-style-type: none"> • manipulable spinal segment established upon motion palpation of the spine (cervical, thoracic and/or lumbar facet syndrome) • and / or sacroiliac syndrome. <p>The exclusion criteria were extensive and ensured that many of the compounding factors that influence IBS as well as influenced the clinical application of manipulation were duly considered.</p> <p>Notwithstanding the above criteria for improving sample homogeneity between the groups, the study had shortcomings which may have restricted the author from drawing more effective conclusions from the results achieved. These include :</p> <ul style="list-style-type: none"> • The use of the antiquated Manning set of criteria (1978), which may not have been comprehensive enough to effectively describe IBS-related symptoms. The use of the Rome Criteria would have been better. • The relatively small sample of 30 (15 per group), which resulted in the use on non-parametric statistics. • The gender ratio of the sample population was described as 4:26 (M:F), this may lend to treatment bias, as it has been shown that women are more receptive to any form of CAM and touch therapies (Van Tilburg <i>et al.</i> 2008; Koloski 2003) which may lead to subjective findings having been reported more favourably. • The use of a randomisation table for the allocation of patients to their respective groups would have strengthened the study. • Self-administered subjective outcome measures employed in this study may not have produced the most reliable results,
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	<p>particularly with the higher proportion of women who may have “expected” the intervention to work and reported such subjectively, albeit unknowingly. This would also, as acknowledged by the author, have been compounded by the “placebo effect” or “touch therapy effect” (Hussain and Quigley 2006).</p> <ul style="list-style-type: none"> • In addition, as with all manual therapies, it is difficult to blind the patient. Therefore, patient naivety could have been considered in recruiting patients for this study, allowing the outcomes of the study to reflect more accurately the clinical outcomes as opposed to perception related to previous exposure to manipulation. • The effect of the practitioner administering both the treatment and providing the outcome measures may have led to an “observer effect” or “Hawthorne effect” (McCambridge <i>et al.</i> 2013) that may have masked the clinical outcomes.
OUTCOME:	<p>The results achieved by this study revealed no discernible difference between the effect of SMT and that of placebo treatment on IBS-related symptoms. Only two participants in the SMT group reported immediate relief of abdominal pain and bloating following spinal manipulation in the T12/L1 region.</p>
DISCUSSION:	<p>Although the results do not support the use of SMT in the management of IBS, the shortcomings observed in the methodology of this study, may have negatively influenced the results achieved. Larger sample size, more experienced practitioner, control measures to negate placebo effects and better assert blinding may have produced a different set of results.</p> <p>Notwithstanding this, the study provides a more rigorous approach to measuring the impact of manual therapy on IBS as a condition when compared to the prior studies (Attali <i>et al.</i> 2013; Brice and Mountford 2000; Florance <i>et al.</i> 2012; Gamber <i>et al.</i> 2002; Hundscheid <i>et al.</i> 2006; Kuttner <i>et al.</i> 2006; Lamas <i>et al.</i> 2009), as it addressed some of the flaws of prior studies, but inadvertently created limitations of its own.</p>

CONCLUSION:	<p>Given the better rigour in this study as compared to the previous discussions (Attali <i>et al.</i> 2013; Brice and Mountford 2000; Florance <i>et al.</i> 2012; Gamber <i>et al.</i> 2002; Hundscheid <i>et al.</i> 2006; Kuttner <i>et al.</i> 2006; Lamas <i>et al.</i> 2009), this study attaining a 9/11 from the reviewers; it provides a basis for future studies to emulate (provided that the inclusion criteria be changed to the Rome Criteria and minor methodological concerns are addressed). In terms of the outcomes of the study, it provides for excellent evidence that manipulation is not an effective form of therapy for patients with IBS.</p>
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Table 4.18	Tabulated feedback data of Article 9:PEDRO Scale					
AUTHOR(S):	PicheT;Pishvaie D; Tirouvaziam D; Filippi J; Dainese R; TonohouhanM; DeGalleani L; Nebot-VivinusM; Payrouse J.L. and Hebuterne X.					
YEAR:	2014					
TITLE:	Osteopathy decreases the severity of IBS-like symptoms associated with Crohn's disease in patients in remission					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	7/11	7/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				100%

Table 4.19 Analysis of Article 9

AUTHOR(S):	PicheT;Pishvaie D; Tirouvaziam D; Filippi J; Dainese R; Tonohouhan M; DeGalleani L; Nebot-Vivinus M.H; Payrouse J.L. and Hebuterne X.							
YEAR:	2014							
TITLE:	Osteopathy decreases the severity of IBS-like symptoms associated with Crohn’s disease in patients in remission							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement
1. Anti-spasmodic consumption: >28 day daily diary. 2. IBS severity: >French validated.. 3. IBDQoL: >Disease-specific questionnaire 4. Fatigue: >FIS questionnaire Depression: >Short version BDI 5. Anxiety: >The Hospital Anxiety and Depression Scale 6. Level of satisfaction: >Overall satisfaction rating with osteopathy. 7. Stool Diary: Frequency and consistency according to the Bristol Scale. >Two 10 day diaries; one for the 10 days prior; another for last 10 days of the study.	Measure 1: Daily record for the duration of 28 days. Measures2 and 3: Assessed on days 0; 15; 30; 45 and 60 of the trial. Measures 4 and 5: Assessed on days 15; 45 and 60 of the trial. Measure 6: Assessed once at the end of the trial. Measure 7: Twice, 10 days leading up to inclusion, and then again over the last 10 days of the trial.	Twelvemonths: Three osteopathic manipulative procedures were performed on days 15, 30 and 45 after the final perfusion of chemotherapy The control group made three visits to the osteopath at the same intervals; they did not receive manipulations. These participants merely received moral support from the practitioner.	38 eligible participants were initially included, with one subject lost from the osteopathy group after one week. Final sample sizes: Osteopathy Group: 25 (16 F, 9 M). Control Group: 12 (8 F, 4 M).	1. No details regarding participant recruitment nor group allocation nor blinding 2. The same osteopathic practitioner applied all the manipulations and the procedure was standardised. 3. Assessor blinding does not apply to this study, as the measures are reported objectively in self-administered questionnaires.	38 participants were randomised using an unequal 2:1 ratio. Control Group: 12 participants assigned to the control group. These patients saw the osteopath on three visits, however, instead of manipulative therapy; they received counselling and moral support only.	Osteopathy Group: 26 participants assigned to this group, (one drop-out a week following inclusion = 25). Patients received osteopathic manipulation : at 15, 30 and 45 days after the final perfusion of infliximab.	7	100%

<p>LIMITATIONS:</p>	<p>Inclusion criteria were extensive and well defined. Crohn's Disease patients were considered in remission if they fulfilled the following criteria: (1) no corticosteroid intake during the previous 12 months; (2) normal GIT mucosa macroscopically identified (colonoscopy); (3) a satisfactory assessment made by a physician based on patient history as well as physical examination; (4) Crohn's Disease activity index of up to 150; (5) Laboratory findings of: C-reactive protein levels below 10mg/l, erythrocyte sedimentation rate below 20mm/h, platelet count below $450 \times 10^{12}/l$, white cell count below $11 \times 10^9/l$. The Rome III criteria were employed to diagnose the presence of IBS related symptoms, which had to be present for more than 25% of the time and reported on for 10 days by means of a daily diary and Bristol stool scale. Criteria needed to be present for at least six months before inclusion, lasting for at least three months.</p> <p>Notwithstanding, these very well defined inclusion criteria, the study was hampered by the relatively small sample size of only 38 (26 with active treatment and 12 controls). This limited sample size has a direct impact on the ability of the researchers to generalise the outcomes of the study to a broader IBS population. This small sample size may also have been affected by the possibility of bias through the type of randomisation that was chosen (consecutive 2:1 randomisation). Therefore it is likely that the inclusion of participants in this study could have been influenced by the researcher, type of patient recruited and place of recruitment (as the latter two are not spelt out clearly in the study).</p> <p>The article does not allow for the reader to determine how many patients were actually screened for inclusion into the study. It is however noted that the authors reported that there was one dropout, but no reasons were given for their exclusion / withdrawal.</p> <p>The lack of a reliable sham osteopathic treatment procedure may have contributed to the inherent short comings of this study (Piche <i>et al.</i> 2014), as the effects of therapeutic touch and perceived intervention (even if it is the attention of a medical professional) has the ability to induce a therapeutic effect (Hussain and Quigley 2006). The researchers argued that the positive findings of a previous sham-controlled study (Florance <i>et al.</i> 2012) provided a basis for using touch as a control. This is however unfounded in that the Florance <i>et al.</i> (2012), showed that after 28 days there was no significant difference between their groups</p>
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(with the article stating that osteopathy is better than sham, without qualifying the time or symptom parameters to which this is actually limited). The intervals between treatment sessions should perhaps be addressed as well, with further investigation into the optimal treatment frequency..

It was noted that all participants received Infliximab at day zero of the study, this administration of a drug known for its use as a treatment modality in IBS patients (Piche *et al.* 2014), may well have been responsible for the changes measured over the 60 period of the study. Although both groups received this intervention, it is not clear why this medication was administered prior to the start of the study intervention and just before / one the day of the administration of the baseline measures. It may well have been better to have one group receive no treatment other than the Infliximab in order to allow effective comparison between the two / three groups.

Further in terms of the intervention, it is unclear as to whether the term “manipulation” referred to the direct, indirect or visceral treatment or all three collectively. This has a direct impact on the reader’s ability to understand whether “manipulation” was applied in three treatment days and / or whether other “non-manipulative” therapy was applied in-between. In addition how this “non-manipulative” therapy subsequently differed from the “caring attention and listening without any manipulation”.

With regards to the treatment, it is acknowledged that the study did provide consistency in the treatment by utilising only one osteopath to provide the treatment. It is however unclear whether this person also provided the “caring attention and listening”. Which, if this was the case, would not have allowed blinding to the treatment intervention, and thereby would not negate the possibility of bias.

In terms of the statistics of this study, the outcomes were predominantly subjective with no objective outcome measures, so the direct effect of the intervention could not be linked to the objective measures and thus directly to the pathophysiology of the IBS.

OUTCOME:	The results of this study, as indicated by the authors, suggest that the “osteopathic manipulation” intervention produced clinically significant amelioration of IBS related symptoms in Crohn’s disease patients in remission. Although levels of fatigue were mildly reduced, no significant changes were observed regarding the degree of anxiety or depression. The clinical effect of osteopathy on IBS related symptoms was sustained during the course of treatment, however this was diminished after the intervention was stopped.
DISCUSSION:	<p>Given the limitations of this study with regards to population representativeness, the influence of the Infliximab as an intervention, the influence of the lack of detailed recruitment and allocation process bias, drop outs and lack of “treater” bias are not excluded as negative influencers and further to this the lack of clarity in terms of the actual intervention further produces confounding factors that may influence the outcomes of the study. Along with the heavy reliance on only subjective measures limits the ability of this study to generalise the outcomes of this study.</p> <p>In addition the effects of the control group intervention cannot be excluded. The clinical condition of IBS has a noted psychological component (Phillips <i>et al.</i> 2014; Tanaka <i>et al.</i> 2011; Drossman <i>et al.</i> 1999) which benefits from the doctor-patient interaction. Therefore, it is not clear that the control intervention was an actual control or non-intervention group (as noted by Florance <i>et al.</i> 2012).As a result it is not possible to accept the outcomes of this study as noted by the researchers without significant caution in addition to noting that their results are only limited to patients that meet their strict inclusion criteria and are concomitantly on Infliximab.</p>
CONCLUSION:	In the context of the reviewers’ score of 7/11, it seems to indicate that the study, although presenting with methodological rigour, has some acute limitations that impact on the outcomes of the study. It is therefore suggested that this study provides moderate evidence in support of osteopathic treatment of IBS patients.

Table 4.20	Tabulated feedback data of Article 10: PEDRO Scale					
AUTHOR(S):	Qu L; Xing L; Norman W; Chen H; Gao S.					
YEAR:	2012					
TITLE:	Irritable bowels syndrome treated by traditional Chinese spinal orthopedic manipulation					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	No	Yes	66%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	No	Yes	Yes	66%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	6/11	6/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				94%

Table 4. 21 Analysis of Article 10

AUTHOR(S):	Qu L; Xing L; Norman W; Chen H; Gao S.							
YEAR:	2012							
TITLE:	Irritable bowel syndrome treated by traditional Chinese spinal orthopaedic manipulation.							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement
1. Visual Analogue Scale (VAS): monitors levels of abdominal pain and discomfort. 2. Bowel Symptom Scale (BSS): reports on abdominal pain or discomfort, bloating, constipation and/or diarrhoea. 3. Symptom Improvement Rating (SIR): reports on the overall effect of the intervention.	1. VAS: Once before treatment resumed and once again at the end of the two week treatment plan. 2. BSS: As with VAS. 3. SIR: Assessed once at the end of the trial.	Two weeks.	210 participants were randomly allocated to one of two intervention groups, resulting in two sample groups of 105 subjects each. Medication Group comprised of 73 female and 23 male. TCSOM Group made up of 73 female and 32 male. No drop outs occurred during the study.	No mention of a specific recruitment method employed. Participants were recruited from the outpatient department of one hospital. Due to the diverse nature of the two interventions allocation, subject and therapist blinding does not apply for this study. No assessor blinding was employed Subjective measuring tools were self administered.	210 participants were randomly allocated to two groups, No detail of randomisation method used <i>Pinaverium Bromide Dicetel group:</i> Participants in the control group received medication in the form of a calcium agonist, prescribed for the relief of IBS related symptoms i.e. abdominal pain, spasm, motility disturbance.	<i>Traditional Chinese orthopaedic spinal manipulation group:</i> Participants in this group each received 5 manipulations over a 2 week period: every other day in the first week, with another on each of every third day in the second week.	7	94%

<p>LIMITATIONS:</p>	<p>The criteria for either inclusion or exclusion to this study were extensive and well defined. These included the following inclusion criteria: The Rome III criteria for the diagnosis of IBS, and with current symptoms, in patients between the ages of 18-60 years. The patients needed to report a VAS with minimum of 20mm distance from the “no symptom” end of the scale. In addition the patients were required to undergo a barium enema or colonoscopy evaluation, along with normal results of the following pathology tests: liver function, full blood count and urea nitrogen and creatinine levels. Lastly, the study required all patients to complete willingly an informed consent letter. In addition to the fairly rigid inclusion criteria, the exclusion criteria as follows allowed for the exclusion of a large number of variant factors that are associated with differential presentations of IBS. This included but was not limited to pregnant / breastfeeding patients, post-menopausal women, any patient with a history of liver disease. In addition the consumption of certain medications e.g. anti-cholinergics, lactulose, smooth muscle relaxants, motility stimulants and anti-depressants resulted in exclusion from the study. More generally, patients with alcohol and/or drug abuse; lactose intolerance; food additive allergies, as well as concomitant inflammatory bowel disease, the presence of gastric and/or duodenal ulcers, a history GI cancers, and celiac Disease and/or diabetes. The contra-indications to orthopaedic manipulation also resulted in exclusion of potential patients.</p> <p>The study’s sample size of 210 participants was adequate in contributing to the use of stronger parametric evaluation of the outcomes, increasing the strength of the conclusions in this study. However with the measurements only being recorded twice during this study, the likelihood in detecting changes becomes more difficult. Gender distribution of the study population was female predominant at ratio 141:68. This ratio does however reflect the demographical observations of IBS patients in the greater population (Lovell and Ford 2012a), which renders the sample population adequately representative of the general population of IBS cases. This may however affect the outcome of the study as female patients are known to respond differently to male patients (Van Tilburg <i>et al.</i> 2008), thus unequal distribution of these genders may provide a source of an outcome that is affected by gender as opposed to the actual clinical outcomes.</p> <p>The manipulations were applied to different spinal levels (T9-L3), according to palpatory findings by the practitioner upon each</p>
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	visit. Thus the study had a lack of a rigidly standardised treatment procedure contributes to the limitations of this study, as it increases the number of subgroups within each of the intervention groups potentially resulting in treatment bias or a possibility that the groups collectively had different sets of interventions resulting in outcomes that are not comparable. The fact that the study duration was a mere 2 weeks hampers its ability to assess any long term effects.
OUTCOME:	The noted results achieved by the authors, indicate that TCSOM was significantly more effective than PBD in the amelioration of IBS related symptoms. Of the 105 subjects in the TCSOM group, 69% reported that their symptoms had disappeared, while 31% reported significant improvement shortly after receiving spinal manipulation. Both VAS and BSS scores were appreciably lower in the TCSOM group compared to those achieved by the PBD group.
DISCUSSION:	The results of this study support not only the theory that TCSOM may be effective in the treatment of IBS and related symptoms, but also the postulated role of vertebral displacement in the manifestation of IBS. The large sample size of 210 adds to the validity of these results, as a result of the use of parametric statistics. However limitations to these outcomes are provided by the variable intervention which was pragmatic and based on patient presentation at each visit. Therefore, further investigation into the exact spinal levels that should be addressed in IBS patients is indicated, in order to establish a more standardised treatment protocol.
CONCLUSION:	As a result of the limitations provided in this study, it was noted that the reviewers awarded the study a 7/11. This along with the qualitative assessment of the study parameters not addressed by the PEDRO scale, indicates that the study's outcome needs to be accepted with caution as the outcome only provide moderate support for the use of TCSOM in the treatment of patients with IBS and that further research addressing this study's shortcomings is necessary.

Table 4.22	Tabulated feedback data of Article 11: PEDRO Scale					
AUTHOR(S) :	Taneja I; Deepak K.K; Poojary G; Acharya I.N; Pandey R.M; Sharma M.P.					
YEAR:	2004					
TITLE:	Yogic versus conventional treatment in diarrhea-predominant irritable bowel syndrome: A randomised control study					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	No	Yes	Yes	66%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	No	No	No	66%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	5/11	6/11	6/11	
		OVERALL PERCENTAGE AGREEMENT:				94%

Table 4.23 Analysis of Article 11

AUTHOR(S):	Taneja I; Deepak K.K; Poojary G; Acharya I.N; Pandey R.M; Sharma M.P.							
YEAR:	2004							
TITLE:	Yogic versus conventional treatment in diarrhea-predominant irritable bowel syndrome: A randomised control study							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement
<p>1. Autonomic Symptom score: Reports on several autonomic symptoms including gastrointestinal disturbance, diarrhoea and abdominal pain.</p> <p>2. Autonomic Functioning: Via parasympathetic reactivity</p> <p>3.. Bowels Symptom Score: Reports on abdominal pain/discomfort, bloating, constipation and/or diarrhoea.</p> <p>4. Gastric motility evaluation: By means of surface electrogastrography recorded by four channel state polygraph.</p> <p>5. Continuous ECG and respiratory function.</p> <p>6. Anxiety evaluation: By means of the State and Trait Anxiety Inventory</p> <p>7. Physical flexibility This evaluation was to ensure that all subjects were flexible enough and capable of holding yoga postures employed in this study.</p>	<p>With the exception of Physical flexibility evaluation, which was measured before the trial commenced, all other measures were reported on at three occasions :</p> <p>Once at the beginning of the study, once one month into the study, and then again at the end of the study one month later.</p>	<p>Two months.</p>	<p>22 males were prospectively recruited and randomly allocated to one of two groups:</p> <p>Conventional group initially consisted of 13 subjects, however one participant was lost before the final follow-up, leaving 12 to the group.</p> <p>Yogic group: Made up of 9 subjects.</p>	<p>Recruitment was via referral from two gastroenterology clinics. -Due to the diverse nature if the two interventions, subject and therapist blinding was not possible. Assessor blinding was not specified, most of the measures reported on via self-administered scoring questionnaires.</p>	<p>Method of randomisation unspecified.</p>	<p>Conventional group: 12 Subjects followed a course of anti-diarrheal medication: 2-6mg of loperamide daily for two months.</p> <p>Yogic group: 9 subjects were to complete a specific yoga routine twice daily for the duration of the two month trial.</p>	<p>6</p>	<p>94%</p>

<p>LIMITATIONS:</p>	<p>The inclusion and exclusion criteria were well defined and included the following: <i>Inclusion</i>: Male aged 20 to 50 years; symptoms of diarrhoea experienced for more than three months, with Rome I criteria applied for the diagnosis of IBS. <i>Exclusion</i> criteria were a good basis for excluding IBS mimicking disease and were described as follows: the presence of other gastrointestinal disease (determined by findings of Barium enema, endoscopy, ultrasound and pathology blood test results; as well as any history of systemic disease e.g. hypertension, diabetes, tobacco use, alcoholism, major psychiatric illness</p> <p>The study population consisted of male subjects only, which inadequately represented the IBS population at large (which has a greater number of women sufferers (Lovell and Ford 2012b); therefore it would be difficult to extrapolate results and findings to the general IBS population. This is further compounded by a small sample size (28 patients). Therefore more rigid methods of randomisation should have been applied, which, however, may not have been practical. The article does not mention the specific method employed to confirm or refute the impact on the results obtained. The article does however indicate that the patients were telephonically screened to ascertain whether they met the Rome I criteria for IBS, increasing the chance for homogeneity which could counteract the small sample size. Notwithstanding this, the relatively small sample size, results in this study lacking statistical power. The lack of power is further compounded by an ill-defined / ill-matched control group.</p> <p>The participants were expected to complete a prescribed yoga routine twice daily for a period of two months. Although measures were in place to ascertain the level of competence and compliance thereby ensuring the subjects' ability to perform the yoga postures; the fact that the intervention was performed by the subjects themselves, in their home environment, raises the concern of uniformity as well as consistency. The length of the trial and the number of "treatment sessions" prescribed may therefore be a limitation of this study.</p> <p>This was identified by the patients, who suggested a more structured, individualized or interactive approach e.g. group classes may motivate individuals to practice yoga daily, at the same time ensuring that the most appropriate postures are held correctly.</p>
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OUTCOME:	Participants in the yoga group described lower anxiety and functional disability levels subsequent to intervention, compared to control group members. After combining pre- and post-intervention data for the two groups, it was found that gastrointestinal symptoms as well as emotion-focussed avoidance, were both lessened by the practice of yoga. All but one participant stated that they planned to continue practicing yoga to manage their IBS related symptoms. It could therefore be reasonably inferred that yoga holds promise as a useful intervention for this population. However, the positive results achieved do indicate the prospects of further research in this field are necessary, particularly addressing the limitations of this and other studies (Kuttner <i>et al.</i> 2006)
DISCUSSION:	Due to exploratory nature of this pilot study p values of 0.1 or less were adopted as worthy of interpretation. Functional disability ($p=0.073$); emotion-focused avoidance ($p=0.09$) and anxiety levels ($p=0.09$) were all key measures that showed significant improvement. This study provides statistically meaningful evidence to support the use of yoga in the management of IBS related symptoms. It could therefore be reasonable inferred that yoga holds promise as a useful intervention for this population.
CONCLUSION:	Pilot studies are inherently limited in their statistical power, however, the positive results achieved not only depicts yoga as a promising treatment option for adolescents suffering from IBS, but also provides rationale for conducting further clinical trials to substantiate the role of yoga in the management of IBS. This is particularly true when assessing the reviewers' outcomes where the rating of the 6/11, provides for moderate evidence in support of yoga.

Table 4.24	Tabulated feedback data of Article 12:PEDRO Scale					
AUTHOR(S):	Tovey P.					
YEAR:	2001					
TITLE:	A single-blind trial of reflexology for irritable bowel syndrome.					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	No	Yes	66%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	Yes	Yes	Yes	Yes	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	Yes	No	66%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	8/11	8/11	8/11	8/11	
		OVERALL PERCENTAGE AGREEMENT:				94%

<p>LIMITATIONS:</p>	<p>This study had inclusion criteria that were well defined, and included diagnosis of IBS as per the Rome Criteria. In addition the exclusion criteria included previous experience with reflexology. This latter exclusion assisted in providing patient naivety, as the patients would not have been able to distinguish between reflexology and foot massage, ensuring optimal subject blinding for improved reliability in the clinical outcomes measuring the treatment effect as opposed to the effect of the patient's knowledge of the intervention. The limitations regarding the inclusion and exclusion criteria were that chronic IBS was not defined and it would seem that systemic disease (e.g. peripheral neuropathy), medication use and wash out periods for medication use were not spelt out explicitly (if they were in the study, this was not provided for in the manner in which the study is currently presented).</p> <p>The small sample size (19 and 15 within the two groups) requires the use of non-parametric statistics, which weakens the statistical analysis of the results. One concern with the sample size is the fact that the authors first indicate that the study required a sample size for an 80% (which is both adequate and required) and then only complete the study with 28 patients. This reinforces the assertion that, although 80% of the patients completed all measures, the study is underpowered and would need to be repeated in order to verify the results obtained. It is not possible to determine whether the groups were homogenous in terms of their demographic characteristics and thus what effect this had on the outcomes of the two groups and their comparison. In addition the lack of description, does not allow for the population in this study to be compared to the population at large, which hampers the ability to extrapolate findings to the general population.</p> <p>The drop-out rate was high especially for the reflexology group. The results seem to suggest that all subjects were lost to the three month follow-up. This raises questions with regards to perceived effectiveness of treatment, perceived ability of the practitioner, effect of the practitioner – patient relationship and other factors that increase compliance (Miller <i>et al.</i> 2006), which may have influenced the outcomes of this study. This also calls into question the optimal trial length and implications for follow up measures in similar such studies.</p>
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In order to minimise the effect of the practitioner – patient relationship the authors of this study made allowance for minimising the placebo effect / treatment based bias associated with the physical interaction between practitioner and subject. In order to do this, the control group subjects received as much physical contact (contact sessions) as the subjects in the intervention group. The recognition of this and amelioration of the placebo effect / treatment bias is important in this study as the outcome measures are all subjective and required the patient to complete subjective outcome measures. Therefore the authors did well to attempt to reduce the impact of perception and its effects on the clinical measures.

However, having stated the above, the study then proceeds with four different practitioners administering treatment. Although there was a written code of conduct for uniformity of the practitioners, there was no statement on training of these practitioners to ensure that they implemented the same protocols in the same way and there was no statement on the qualifications of the practitioners treating the participants and whether or not they were comparable in their approach.

To compound the effect of the small sample size, and issues of statistical power, there is a lack of clarity in the relationship between the HAS and the diary, as well as when they were recorded relative to one another. This makes it difficult to understand how these outcome measures relate to one another and whether the recorded effects support each other or not. Further to this, it was not clear as to who was responsible for noting the outcome measures. From the lack of a description, it would suggest that the person completing the outcome measures was a practitioner responsible for the treatment, thus decreasing blinding, increasing the “Hawthorne” or “Observer” effect (McCambridge *et al.* 2014) and increasing bias recorded in the outcome measures. In terms of the actual “sham” intervention, the effect of touch therapy provided for through the “foot massage” cannot be taken as a non-clinical intervention. Therefore it is possible that the “sham” group could have improved to the same extent as the actual intervention group.

OUTCOME:	Based on results achieved in this trial, there is no substantiated evidence that reflexology is effective in the amelioration of IBS related symptoms. There was no statistical or clinically significant difference in the outcome between the two groups for the following measures: abdominal pain, constipation/diarrhoea and abdominal distension.
DISCUSSION:	<p>According to the postulated reflexology theory, the intervention group was expected to benefit from the treatment with ensuing relief of IBS related symptoms. However results achieved proved to the contrary. It is difficult to agree with the study's results and, based on the following grounds, it's conclusions remain questionable:</p> <ul style="list-style-type: none"> - Groups may not have been comparable, in terms of gender and the duration of symptoms, - No exclusion of possible systemic disease as confounders were noted in the article, - No implied or stated consistency between the practitioners was presented, - No qualifications noted for the practitioner implementing treatment was provided, - No indication that the measures were not taken by the person treating – to exclude the Hawthorn / observer effects, - A very small sample size that is underpowered given the <i>a priori</i> analysis - High level of attrition in participant numbers. Out of a sample size of 34, six were lost to drop-outs. The reasons for these drop outs were not included in the publication.
CONCLUSION:	Notwithstanding the qualitative limitations of the study that were identified above, the reviewers provided an 8/11 scoring for this particular study. This rating is however compromised with the low sample size, possible lack of homogeneity of the sample groups and the manner in which the treatment was applied, and finally the results achieved. The results achieved in this article provides no evidence in support of reflexology in the treatment of IBS.

Table 4.26	Tabulated feedback data of Article 13: PEDRO Scale					
AUTHOR(S):	Xing L; Qu L; Chen H; Gao S.					
YEAR:	2013					
TITLE:	A clinical observation of irritable bowel syndrome treated by traditional Chinese spinal orthopaedic manipulation					
CRITERION:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	Yes	No	Yes	Yes	66%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	TOTAL SCORE	7/11	6/11	7/11	7/11	
		OVERALL PERCENTAGE AGREEMENT:				97%

Table 4.27 Analysis of Article 13

AUTHOR(S):	Xing L; Qu L; Chen H; Gao S.								
YEAR:	2013								
TITLE:	A clinical observation of irritable bowel syndrome treated by traditional Chinese spinal orthopaedic manipulation								
STUDY PROPERTIES:									
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 11	Total Percentage Agreement	
1. Bowel Symptom Scale (BSS): reports on abdominal pain or discomfort, bloating, constipation and/or diarrhoea via VAS. 2. Symptom Improvement Rating (SIR): reports on the overall effect of the intervention. 3. Patient Self Assessment (PSA): Evaluates the effect of the therapy.	1. VAS: Once before treatment resumed and once again at the end of the two week treatment plan. 2. BSS: As with VAS. 3. SIR and PSA Assessed once at the end of the trial period.	Two weeks	60 participants were recruited from the outpatient department of a hospital. These were randomly allocated to one of two intervention groups, resulting in two sample groups of 30 subjects each. Medication group comprised of 12 men and 18 women; while the TCSOM group included 13 men and 17 women. There were no losses to drop outs in this study.	-No mention made of a specific recruitment method employed. Participants were recruited from the outpatient department of one hospital. -Due to the diverse nature of the two interventions allocation, subject and therapist blinding does not apply for this study. -No assessor blinding either, as the subjective measuring tools were self administered.	60 participants were randomly allocated to two groups, No detail of randomisation method used	<i>Pinaverium bromide Dicetel group:</i> Participants in the control group received medication in the form of a calcium agonist, prescribed for the relief of IBS related symptoms i.e. abdominal pain, spasm, motility disturbance.	<i>Traditional Chinese orthopaedic spinal manipulation group:</i> Participants in this group each received 5 manipulations over a 2 week period: every other day in the first week, with another on each of every third day in the second week	7	97%

<p>LIMITATIONS:</p>	<p>Criteria for either inclusion or exclusion to this study were extensive and well defined.</p> <p>Inclusion criteria included the following: the Rome III criteria for the diagnosis of IBS, and with current symptoms, as applied to patients between the ages 18-60 years, who were willing to sign an informed consent form; with a VAS reporting a minimum of 20mm distance from the “no symptom” end of the scale. The patients were required to undergo a barium enema or colonoscopy evaluation. In addition they were required to be within normal parameters for the following pathology tests: liver function, full blood count and urea nitrogen and creatinine levels. The exclusion criteria, ensured the exclusion of all extraneous factors that could mimic as IBS and provided for a safe clinical environment in which manipulative therapy could be administered. These criteria therefore ensured a relatively significant level of homogeneity between the groups in the study.</p> <p>However the study’s relatively small sample size resulted in an underpowered study, which may have impacted on the conclusions drawn by the authors. In addition the measurements were only reported on twice during this study. Although simplistic in design, this aspect of the methodology may be a limitation, in that it provides for limited interpretation of the results. To compound this, the interventions of TCSOM were applied at different spinal levels (T9-L3), according to palpatory findings by the practitioner upon each visit. This implies that it is possible that the 30 patients in the TCSOM group may each have received an individual treatment plan based on the combination of the TCSOM manipulation combinations applied at each visit. The lack of a rigidly standardised treatment procedure contributes to the limitations of this study, as it is tantamount to a case series being compared to a control group. This mix of intervention possibilities also limits the ability of TCSOM from being identified as a specific modality within a specific region of the spine as being superior or inferior to the control group.</p>
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OUTCOME:	As indicated by the authors, the results achieved indicate that TCSOM was significantly more effective than PBD in the amelioration of IBS related symptoms. Of the 30 subjects in the TCSOM group, 23 reported that their symptoms had disappeared, and 6 reporting or significant improvement shortly after receiving spinal manipulation. Both VAS and BSS scores were appreciably lower in the TCSOM group compared to those achieved by the PBD group.
DISCUSSION:	<p>Given the limitations provided for outside of the PEDRO evaluation sheet (Table 4.26), it is necessary to consider that the outcomes of the study may be limited, particularly as it requires the expertise of the practitioner to not only find, but also correct the spinal fixations as addressed by the TCSOM. Along with the intervention variance, it may not be possible to consider that manipulation (TCSOM) of a particular spinal region to be useful in the treatment of TCSOM. This would require a further study that investigates spinal fixations within the IBS population before sub populations are identified and clinical prediction rules are determined.</p> <p>Another limitation in comparing medication to manual therapy is that they have different mechanisms of action so the appropriateness of the measurement tool in assessing outcomes becomes important as it is required to measure the effects of both interventions. It may therefore be necessary to consider running TCSOM against touch therapy, massage or another manual therapy in order to determine its clinical effectiveness.</p> <p>It has to be emphasised that the methodology of this article is exact in terms of a previous study by the same authors (Qu et al. 2012), its results would then best serve as an affirmation of the role of TCSOM in the management of irritable bowel syndrome.</p>
CONCLUSION:	The results of this study supports not only the theory that TCSOM may be effective in the treatment of IBS related symptoms, but also the postulated role of vertebral displacement in the manifestation of IBS. However given the limitations and the 7/11 rating (both indicating moderate support for TCSOM as an intervention in IBS), further investigations into the exact spinal levels to be manipulated, needs to be addressed. This could lead to the establishment of a more standardised treatment protocol, as well asserting the postulation that vertebral displacement may contribute to IBS. Therefore this study only provides moderate support for TCSOM in the management of IBS.

4.4.2 Non-randomised clinical trials

The Newcastle Ottawa Scale: Appendix G (Wells *et al.* 2011) was used to grade the three non-randomised clinical trials that were included in this systematic review. In short, this scale comprises 8 criterion points, apart from point 5 (addressing comparability) which has a two point allocation, each of the other points can receive a maximum of a one point score. The maximum points awarded could therefore be 9.

Table 4.28 List of table numbers for nRCTs arranged in alphabetical order.

Tabulated feedback data:	Analysis of article:	Author(s):	Year:	Title:
Table 4.29	Table 4.30	Brands M.M.M.G; Purperhart H; Deckers-Kocken J.M.	2011	A pilot study of yoga treatment in children with functional abdominal pain and irritable bowel syndrome
Table 4.31	Table 4.32	Perrin R.N; Edwards J and Hartley P.	1998	An evaluation of the effectiveness of osteopathic treatment on symptoms associated with Myalgic Encephalomyelitis. A preliminary report
Table 4.33	Table 4.34	Pizzolorusso G; Turi P; Barlafante G; Cerritelli F; Renzetti C; Cozzolino V; D'Orazio M; Fusilli P, Carinci F. and D'Inecco C.	2011	Effect of osteopathic manipulative treatment on gastrointestinal function and length of stay of preterm infants: an exploratory study

Table 4.29	Tabulated feedback data for Article 14: NOS					
AUTHOR(S):	Brands M.M.M.G; Purperhart H; Deckers-Kocken J.M.					
YEAR:	2011					
TITLE:	A pilot study of yoga treatment in children with functional abdominal pain and irritable bowel syndrome					
CRITERIA:¹		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
Selection:	1. Is the case definition adequate?	1	1	1	1	100%
	2. Representativeness of the cases	1	0.5	1	1	66%
	3. Selection of controls	0	0	0	0	100%
	4. Definition of controls	0	0	0	0	100%
Comparability:²	5. Comparability of cohorts on the basis of design or analysis	1	0.5	1	1	66%
Exposure:	6. Ascertainment of exposure	1	0.5	1	1	100%
	7. Same method of ascertainment for cases and controls	1	1	1	1	100%
	8. Non-response rate	0	0	0	0	100%
	TOTAL SCORE OUT OF 9	5	3.5	5	5³	92%

¹ For ease of reference, the eight criteria have been labelled one to eight in Section 4.2.2. This is in contrast to the Newcastle-Ottawa Scale (Wells *et al.*, 2003) which delineates the questions per criterion (viz. selection, comparability and exposure).

² This is the only criterion which has a two point allocation.

³ The score calculated for the study, is derived from the majority score of the three reviewers, and not a mean calculation of the three individual reviewer total scores.

Table 4.30 Analysis of Article 14

AUTHOR(S):	Brands M.M.M.G; Purperhart H; Deckers-Kocken J.M.							
YEAR:	2011							
TITLE:	A pilot study of yoga treatment in children with functional abdominal pain and irritable bowel syndrome							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 9	Total Percentage Agreement
1. Abdominal Pain Diary (APD): Reports on pain frequency and intensity. 2. Abdominal pain yoga questionnaire: Reports stool patterns and frequency of abdominal discomfort. 3. Kidscreen-27 Quality of Life Questionnaire: Reports physical, psychological and social wellbeing. 4. Child Behavioural Checklist: Completed by the parent, it rates the child's emotional and behavioural struggles.	T0: Baseline one month before treatment commenced. T1: One week before treatment. T2: Directly following the last session. T3: Three months after the last session. Questionnaires were completed at the following intervals: -Abdominal pain yoga questionnaire at T0 and T2. -Kidscreen-27 at T0, T1, T2 and T3. -Child Behaviour Check List at T0 and T2. Abdominal pain diary: Completed daily during baseline period, for a month leading up to T2, and for the month leading up to T3.	One month baseline period, twelve weeks treatment period and three month follow-up period. Seven months in total.	20 children (11 boys and 9 girls) were divided in to two groups according to their age groups: 10 subjects in the 8-11 year old group, 2 drop outs = 8. 10 subjects in the 12-18 year old group, 1 drop out = 9. Resultantsample size of 17, partial drop out reporting.	This was an unblinded study.	None	None	5	92%

<p>LIMITATIONS:</p>	<p>In this study, the inclusion criteria were principally based on age (8 to 18 year olds), and a diagnosis of functional abdominal pain (FAP) and/or IBS in accordance with the Rome III criteria. Further it was required that no participant had previously received yoga therapy, relaxation therapy, hypnotherapy or psychotherapy for their condition, to be included. Considering that the study focussed on children and required parental consent, it was likely that the sample size would have been limited. Given these limitations, this study had a small sample size which resulted in an underpowered / undervalued statistical outcome to the study. This was additionally compounded by the 15% drop out rate.</p> <p>Although cognizance was made of the possible placebo effect in IBS patients, no control measures were employed to minimise this effect. This in addition to the nature of the intervention and the absence of a control made for an un-blinded study design. A baseline period was integrated into the study design. During this one month period of standard care only, measurements ensured that the patients could serve as their own controls.</p> <p>A further confounding factor is that the majority of the reporting mechanisms (with the exception of one) were to be completed by the children. It is possible to consider that a child aged 12 or older may be in a position to accurately record improvement / lack of improvement in their condition, an ability potentially limited in children younger than 12 years of age [National Health Act, No 61 (Zuch <i>et al.</i> 2012)]. This lack of attention to data feedback is possibly the largest of the limitations of this study, especially in terms of memory decay in children, where time is often inconsequential (Mouton, 2006). It may actually be necessary to consider developing more child friendly reporting data sheets that are able to extract more accurate and reliable data in terms of time and symptomatology over time.</p>
<p>OUTCOME:</p>	<p>Both age groups reported a significant decline (compared to baseline values) in pain <i>frequency</i> by the end of the treatment period. Pain <i>intensity</i> had significantly reduced in the younger age group at this stage. At the follow-up assessment three months later, a significant reduction in pain intensity as well as pain frequency found to have persisted in the younger group, at the same time, the older group reported a marginally significant reduction in pain frequency alone. Parents of the participants reported significant increases in the quality of life of these children, irrespective of age.</p>

	Therefore the results achieved in this pilot study would seem to support the use of yoga in the treatment of functional abdominal pain and IBS in children aged 8 to 18. Medium term effects, persisted for a period of at least three months, were found to be more significant in those aged 8 to 11.
DISCUSSION:	Although positive results were achieved, conclusions must be drawn with significant caution. The study's limitations, although well described, hamper the ability to produce rigorous statistical evidence in support of the yoga intervention. It does however produce anecdotal evidence in support of yoga, with indication for further research on the topic.
CONCLUSION:	Given the reviewers scoring of a 5/9, it suggests that the nRCT has a significant problem in terms of its scientific rigour, which complements that limitation noted in a qualitative assessment of the article beyond those criteria outlined in the reviewer rubric. As a result the outcomes of this study need to be read with caution, indicating that the evidence that this article provides in terms of yoga for children between the ages of 8-18 is at best limited and requires further diligent study in the form of a RCT or a more rigorous nRCT in order to provide conclusive evidence in favour of treating children with IBS utilising this mode of intervention. This study therefore only provides limited evidence in favour of the intervention.

Table 4.31	Tabulated feedback data of Article 15: NOS					
AUTHOR(S):	Perrin R.N; Edwards J; Hartley P.					
YEAR:	1998					
TITLE:	An evaluation of the effectiveness of osteopathic treatment on symptoms associated with Myalgic Encephalomyelitis. A preliminary report					
CRITERIA:⁴		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
Selection:	1. Is the case definition adequate?	0.5	0.5	1	0.5	66%
	2. Representativeness of the cases	1	1	0.5	1	66%
	3. Selection of controls	1	1	0.5	1	66%
	4. Definition of controls	0	0	0	0	100%
Comparability:⁵	5. Comparability of cohorts on the basis of design or analysis	1	1	1	1	100%
Exposure:	6. Ascertainment of exposure	0	0	0	0	100%
	7. Same method of ascertainment for cases and controls	1	1	1	1	100%
	8. Non-response rate	0	0	0	0	100%
	TOTAL SCORE OUT OF 9	4.5	4.5	4.5	4.5⁶	87%

⁴ For ease of reference, the eight criteria have been labelled one to eight in Section 4.2.2. This is in contrast to the Newcastle-Ottawa Scale (Wells *et al.*, 2003) which delineates the questions per criterion (viz. selection, comparability and exposure).

⁵ This is the only criterion which has a two point allocation.

⁶ The score calculated for the study, is derived from the majority score of the three reviewers, and not a mean calculation of the three individual reviewer total scores.

Table 4.32 Analysis of Article 15

AUTHOR(S):	Perrin R.N; Edwards J and Hartley P.							
YEAR:	1998							
TITLE:	An evaluation of the effectiveness of osteopathic treatment on symptoms associated with Myalgic Encephalomyelitis. A preliminary report							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 9	Total % Agreement
1. General Health Questionnaire: Assessed 26 symptoms commonly suffered by ME patients. 2. Back pain questionnaire : To establish a possible association between back pain and severity of ME-related symptoms. 3. Revised Back Depression Inventory. 4. The Beck Anxiety Inventory. 5. The Morgan Gledhill Sleep questionnaire: assessed abnormal sleep patterns, a cardinal symptom of ME.	Questionnaires 1 – 8 were completed every three months over the course of the twelve month study period. The laboratory measurements of fatigability and spinal mobility were performed at the start of the study and once every six months thereafter, three readings in total.	Twelve months.	Initially 80 participants were included. - Forty participants were allocated to the osteopathic group, five did not pass the Action for ME questionnaire. One participant could not participate due to unforeseen travel abroad, resulting in a final sample of 34. - The initial control group number of 40 participants was diminished to 23 over the course of the twelve month study period. There is inconsistency in the	Blinding was not noted in this study. -Control group subjects requested to receive treatment, while control group subjects voluntarily agreed to be part of this group. - No mention was made of who performed the objective laboratory testing for fatigability and spinal mobility, nor whether they were aware of which groups the respective subjects belonged to. -Subjective outcome measures in the form	Control Group: Participants received no manual therapy, instead they could select any other treatment available for ME. Patient Group: Twenty sessions of osteopathic treatment was prescribed over a twelve month period.	N/A	4.5	87%

<p>6. Broadbent's cognitive functioning questionnaire: Reduced cognitive functioning in ME patients has been found in ME patients while trying to complete mental performance tests.</p> <p>7. The Nottingham Health Questionnaire: assesses general ME symptoms.</p> <p>8. The profile of fatigue related states.</p> <p>9. Fatigability: Laboratory assessment of knee extensor muscle fatigability.</p> <p>10. Spinal mobility: The Salford Biomechanical Workstation was employed to digitise thoracic spinal movement from video film, calculating the maximum extent of spinal flexion achieved in active full flexion.</p>			<p>report as to final participant numbers:</p> <p><i>Patient selection: page 2 describes a total of 58, [34 osteopathic, 24 control] study participants. However, on page 6 the control group is mentioned to include a final count of 23.</i></p> <p><i>Adding to the inconsistency, is the gender ratio of the patient group stated as 22:11 (F:M), implying a total of 33 participants in the patient group.</i></p> <p><i>Control group gender ratio given as 17:7 (F:M).</i></p>	<p>of eight self-administered questionnaires were employed to monitor participants' response to the interventions, while two measures were assessed objectively in a clinical environment.</p>					
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<p>LIMITATIONS:</p>	<p>Although this study pertains to myalgic encephalomyelitis (ME), reported symptoms included irritable bowel syndrome (Perrin at al. 1998), which provided justification for inclusion in this systematic review, as suggested by fellow reviewers who participated in this SR. Furthermore, ME is classified as a functional disorder and manifests in 51% of IBS patients. As with fibromyalgia, some clinicians believe that these conditions should be grouped together under the single “umbrella” term of <i>functional somatic syndromes</i> (FSS) (Heningsen <i>et al.</i> 2007).</p> <p>Criteria for inclusion to, or exclusion from this study were extensive and well defined as the following:</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> ➤ Ages 18 to 55. ➤ London criteria for diagnosis of ME. ➤ Financial ability to afford the treatment over the one year period. ➤ Ability to travel to and from the treatment clinics. ➤ The intention to continue treatment for the entire duration, however, participants were allowed to abandon the study at any point in time. ➤ Willingness to participate in a lengthier follow-up trial. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> ➤ Applicable only to the patient group: <ul style="list-style-type: none"> • any other form of ME treatment started within the 6 months prior to inclusion to this study. ➤ Applicable to both groups: <ul style="list-style-type: none"> • any manual therapy other than that from this study’s author. ➤ Pre-morbid depression symptoms. ➤ Indication of psychiatric disorders, or family history thereof. ➤ Positive test for other unaddressed causes of symptoms.
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- Any other form of neurological pathology.

Factors that contribute to the limitations of this study included the following:

- This was a non-randomised study, with participants electing which group they would be allocated to. Eighty volunteers were initially included, with 40 specifically requesting osteopathic treatment, while the other 40 volunteered to be allocated to the control group. This negated the use any blinding methods in the study. This provides patient bias and excludes naivety as the patients have an inherent expectation when entering the study (given that they expect a certain outcome from the group that they chose).
- The final number of participants' remains unclear, either 58, 57 or 56 in total. This calls into question the accuracy of recording, data analysis and reporting. There may well be an explanation for the differences, however these are not provided by the authors.
- The gender ratio of the groups was female predominant, although in line with global prevalence rates, this can be considered a limitation. Female subjects have been found to be more receptive to CAM and touch therapies (Van Tilburg et al. 2008; Koloski 2003), which may have influenced the results of this study, possibly leading to intervention bias.
- On a positive note, this study, unlike many of the prior studies included both objective as well as subjective outcome measures to assess participant response to the various treatment modalities.
- The familiar placebo effect of manual therapies (Hussain and Quigley 2006) was not addressed in this study, with no measures employed to minimise the effect.

OUTCOME:	<p>The results obtained for this study revealed a remarkable amelioration of ME symptoms following one year of osteopathic treatment. Statistical evidence indicated that osteopathic treatment had a superior effect on ME symptoms compared to the effects documented by the control group subjects. This evidence was based on the reported (positive) effects on the following (most significantly observed in the patient group) :</p> <ul style="list-style-type: none"> • Depressive symptoms, anxiety and sleep levels. • Back pain • Cognitive functioning • Fatigue related states and muscle fatigue resistance
DISCUSSION:	<p>Although the study seems to provide outcomes that are suggestive of osteopathic care being able to achieve significant clinical outcomes, it is important to remember that the limitations of the study noted above may have had a significant impact on the outcome. The most important of these limitations would have been the ability of the patients to choose their intervention. Patients that are not naïve in terms of the intervention and are prepared to try a new intervention for their therapy are likely to report improved findings to a greater extent than those patients that were allocated to / elected to accept the medication only group (as this group is likely to have previously experienced medication as not helping and may therefore underreport any improvements). The latter would then serve to amplify the former. This assertion is particularly true in face of the fact that 4/5 outcomes that improved significantly are subjective in nature and only one is objective (however muscle fatigue can be influenced by how the patient feels and to what extent they are prepared to participate in the measurement process).</p> <p>The above lack of perception management and its influence is compounded by the lack of clarity in the methodology, which brings about speculation as to the accuracy of patient tracking, recording, data analysis and reporting.</p>
CONCLUSION:	<p>In conclusion, the above ambiguity in the article can be seen in the low rating (4.5/9) as well as the relatively low level of agreement between the examiners (87%). This suggests that the article as it is presented is unclear as to the outcomes being measured by the reviewers scale (Liddle Scale: Appendix I). Therefore given the limitations of the study and the low ranking by the reviewers, this article provides for limited evidence in support of osteopathy as an intervention in the treatment of symptoms associated with ME.</p>

Table 4.33	Tabulated feedback data of Article 16: NOS					
AUTHOR(S):	Pizzolorusso G; Turi P; Barlafante G; Cerritelli F; Renzetti C; Cozzolino V; D'Orazio M; Fusilli P, Carinci F. and D'Inecco C.					
YEAR:	2011					
TITLE:	Effect of osteopathic manipulative treatment on gastrointestinal function and length of stay of preterm infants: an exploratory study					
CRITERIA:⁷		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
Selection:	1. Is the case definition adequate?	1	0.5	1	1	66%
	2. Representativeness of the cases	1	0.5	1	1	66%
	3. Selection of controls	1	1	1	1	100%
	4. Definition of controls	1	1	1	1	100%
Comparability:⁸	5. Comparability of cohorts on the basis of design or analysis	1	2	1	1	66%
Exposure:	6. Ascertainment of exposure	1	1	1	1	100%
	7. Same method of ascertainment for cases and controls	1	1	1	1	100%
	8. Non-response rate	0	0	0	0	100%
	TOTAL SCORE OUT OF 9	7	7.5	7	7⁹	87%

⁷ For ease of reference, the eight criteria have been labelled one to eight in Section 4.2.2. This is in contrast to the Newcastle-Ottawa Scale (Wells *et al.*, 2003) which delineates the questions per criterion (viz. selection, comparability and exposure).

⁸ This is the only criterion which has a two point allocation.

⁹ The score calculated for the study, is derived from the majority score of the three reviewers, and not a mean calculation of the three individual reviewer total scores.

Table 4.34 Analysis of Article 16

AUTHOR(S):	Pizzolorusso G; Turi P; Barlafante G; Cerritelli F; Renzetti C; Cozzolino V; D’Orazio M; Fusilli P, Carinci F. and D’Inecco C.							
YEAR:	2011							
TITLE:	Effect of osteopathic manipulative treatment on gastrointestinal function and length of stay of preterm infants: an exploratory study							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking out of 9	Total Percentage Agreement
1. Gut symptom frequency: -via clinical charts completed by NICU nursing staff. -Assessed the incidence of vomiting, regurgitation, gastric reflux, frequency of stool. 2. Excessive duration of length of stay in NICU	Symptoms were assessed twice weekly (Tuesdays and Fridays), for the entire period of hospital stay.	Relative to each neonatal subject.	350 consecutive preterm infants that were admitted to NICU, without major complications: 162 subjects were allocated to the osteopathy group (81 males, 81 females). 188 subjects allocated to the control group (99 males, 89 females).	No mention was made specifically as to assessor blinding methods, only that data collection was done by undergraduate osteopaths.	The control group received routine neonatal care only. This protocol followed standardised guidelines as to feeding regimes and glucose-glycerin enemas. Enemas were administered twice daily until at least one spontaneous stool passage occurred.	The intervention group received OMT in addition to routine neonatal care received by the control group.	7	87%

<p>LIMITATIONS:</p>	<p>The inclusion of this article is based on recommendations made by fellow reviewers who took part in this systematic review. One of the outcomes included frequency of stool, the number of enemas administered to the subjects to address the functional constipation in pre-term neonates. As discussed in section 2.2.5, the symptoms of functional constipation and IBS-C are so similar that the viability of the existing “artificial division” between these two FGIDs is disputed (Suarez and Ford 2009).</p> <p>All neonates consecutively admitted to the NICU of the public hospital in Pescara, Italy between January 2005 and June 2008, were eligible for <i>inclusion</i> to this study. GI dysfunctions that are commonly observed in pre-term neonates include functional constipation and hard stools, vomiting, regurgitation and gastric reflux.</p> <p><i>Exclusions</i> were made based on the following criteria:</p> <ul style="list-style-type: none"> • Gestational age less than 29 weeks or greater than 37 weeks. • Osteopathic treatment received more than two weeks following birth. • Neonates transferred to or from other hospitals and/or units. • Neonates from HIV-positive or drug abusive mothers. • Genetic and/ or congenital disorders. • Cardiovascular disorders. • Neurological disorders. • Suspected or confirmed necrotizing enterocolitis with or without gastrointestinal perforation. • Suspected or confirmed abdominal obstruction. • Pre- and/or post-surgery patients. • Pneumoperitoneum and/or atelectasis. <p>The following shortcomings were identified to this particular study:</p>
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	<ul style="list-style-type: none"> - This was a non-randomised clinical trial, in which the patient were consecutively allocated to their respective groups (i.e. there was no randomisation process). - Although the sample size of 350 seemed adequate to produce statistically significant result (i.e. the study was not underpowered), the fact that participants were of neonatal age and recruited from only one NICU means that the sample population was not representative of the greater population of cases, unless they conform specifically to the inclusion and do not fit any exclusion criteria as noted above. - Lacking in rigor, outcome measures employed may not have been comprehensive enough, and therefore may have produced variable results. This is particularly true in that it relied on the nursing staff to complete data sheets in addition to their standard workload, after which undergraduate osteopaths reviewed the charts and documented findings (it is not stated if there was any missing data that would have excluded any of the potential participants). - The OMT was applied according to the practitioner's palpatory findings on each examination and this implies that it is likely that each of the neonates received their own "standard care", which was not consistent across all the neonates receiving osteopathic care. A better standardised osteopathic procedure for all participants would arguably produce more reliable results, but it is acknowledged that this would be less pragmatic (applicable to clinical practice). - Relevant variables that were not considered in this study include delivery factors, breastfeeding, respiratory support, feeding methods as well as gastric emptying times. All of these factors may have influenced the outcome of this study.
OUTCOME:	The authors report that the statistical analysis of the results obtained, produced evidence in support of osteopathic treatment of gastrointestinal dysfunction in preterm infants. OMT was confirmed to be independently linked with a 55% reduction in GI symptoms, as well as more than 75% reduction in excessive length of stay.
DISCUSSION:	Although this study had some significant methodological positives, including the criteria for admission onto the study, the nursing staff (potentially blinded) recording the data (with interns subsequently reviewing the charts and extracting the required data), both of which were independent of the osteopath treating the neonates, allowing for blinding of each of the parties; it is necessary to indicate that the lack for intervention standardisation makes this study impossible to be reproduced. In addition the lack of controlling for factors that may have influenced gastric function sets another limitation.

CONCLUSION:	<p>Limitations aside and considerations of the reviewers' outcome (7/9), this study managed to produce evidence that strongly suggest that osteopathic treatment has an effect on neonate gastrointestinal function (including functional constipation and hard stools which usually requires the use of enemas). This study therefore provides excellent levels of evidence in support of osteopathic treatment for the population under study and indicates a need for further, more rigidly designed clinical trials in this field. The limitations described in this publication themselves could set ground for new development in both clinical and research fields.</p>
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4.4.3 Case studies and case reports

The remaining two articles included in this systematic report (one being a case study, the other a case report) were ranked according to scores achieved applying the Liddle Scale: Appendix I (Liddle *et al.* 1996).

Table 4.35 List of Table numbers for Case Studies/Reports

Tabulated feedback data:	Analysis of article:	Author(s):	Year:	Title:
Table 4.36	Table 4.37	Amalu W.C.	1998	Autism, Asthma, Irritable Bowel Syndrome, Strabismus, and Illness Susceptibility: A Case Study in Chiropractic Management
Table 4.38	Table 4.39	Wagner T; Owen J. and Malone E.	1995	Irritable bowel syndrome and spinal manipulation: a case report

Table 4.36 Tabulated feedback data of Article 17: LIDDLE SCALE

AUTHOR(S):		Amalu W.C.					
YEAR:		1998					
TITLE:		Autism, Asthma, Irritable Bowel Syndrome, Strabismus, and Illness Susceptibility: A Case Study in Chiropractic Management					
CRITERION:			Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Are the study participants well-defined in terms of time, place and person?		B1	B1	B1	B1	100%
2	What percentage of individuals refused to participate?		n/a	n/a	n/a	n/a	100%
3	Are outcomes measured in a standard, valid and reliable way?		A	A	B2	A	66%
4	Are outcomes measured in the same way for both intervention and control groups?		n/a	n/a	n/a	n/a	100%
5	Are factors other than intervention comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?		n/a	n/a	n/a	n/a	100%
6	What percentage of individuals recruited into the study are not included in the analysis?		n/a	n/a	n/a	n/a	100%
7	Is the analysis by intention to intervene (treat)?		A	A	A	A	100%
8	Are results homogenous between sites?		n/a	n/a	n/a	n/a	100%
9	How well was the study done to minimise bias?		C	C	B2	C	66%
10	Is the overall effect of the study due to the study intervention?		B2	B2	B2	B2	100%
11	Explain if there is any practical/ethical reason why an RCT cannot be done?		A	B2	A	A	66%
	TOTAL SCORE		A:3 B1:1 B2:1 C: 1` I:0 n/a:5	A:2 B1: 1 B2: 2 C:1 I: 0 n/a: 5	A:2 B1:1 B2:3 C:0 I:0 n/a: 5	A:2 B1:1 B2:2 C:1 I:0 n/a:5	91%

Table 4.37 Analysis of Article 17

AUTHOR(S):	Amalu W.C.							
YEAR:	1998							
TITLE:	Autism, Asthma, Irritable Bowel Syndrome, strabismus, and Illness Susceptibility: A Case Study in Chiropractic management							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking	Total Percentage Agreement
1.Paraspinal digital infrared thermal imaging was employed to determine affected spinal levels, as well as to assess the effect of spinal manipulation on the dysfunctional levels. 2. The effect of SMT on the symptomatology of the patient was solely reported on by the patient's mother.	1. Upon initial consult a full spinal thermal imaging was performed. Cervical thermal imaging was repeated at the beginning of each subsequent visit, as well as after each manipulation performed. After 4 weeks another full spinal thermal image was taken. 2. The patient's mother reported on changes in symptomatology on every visit: once at the end of weeks one, two, three, four, six and eight, nine to twelve.	Twelve weeks	One five year old female.	Blinding is not applicable in this case.	None. Spinal manipulation was the only intervention applied.	Single case study.	A : 2 B1: 1 B2: 2 C : 1 I : 0 n/a: 5	91%

LIMITATIONS:	<p>The inherent limitations typically associated with single case reports include:</p> <ul style="list-style-type: none"> • A sample size of one, • No controls employed and • No blinding applicable. <p>Furthermore, in this particular study, the diagnosis of IBS could not be confirmed to be in accordance with the universally applied Rome criteria, which provides for doubt as to the reliability of the initial diagnosis (although the clinical experience of the author may have provided the correct diagnosis).</p> <p>The effect of SMT on the patient's bowel related symptoms was solely reported on by the patient's mother at each visit. No mention was made of any formal logging of symptom frequency and severity through the regular completion of a diary or other mechanism.</p> <p>The use of the thermal imaging device although often utilised in clinical practice has limited evidence (reliability, sensitivity and specificity) to show that it is able to detect the appropriate spinal lesions that would require manipulation. It is therefore uncertain as to whether the manipulated segments actually required manipulation as indicated by this unit. Also the use of this device assumes that there is a relationship between the patient's pathologies and the thermal imaging device identified lesion that is then manipulated.</p>
OUTCOME:	<p>The author reports that the results of the paraspinal infrared imaging, showed near complete resolution of neuropathophysiology by the fourth week of treatment. Post-treatment thermal imaging of the cervical spine showed correction of subluxations by spinal manipulation. As far as the patient's IBS-like diarrheal episodes, these were reported on weekly for 12 weeks. By the end of week 3, the patient's mother noted that bowel symptoms had improved from profuse diarrhoea four times a day, to once or twice daily. By the end of week four, only one loose stool daily occurred. Continuous improvement in bowel symptoms was noted over the following eight weeks, by end week twelve, the IBS had near completely resolved.</p>

DISCUSSION:	<p>The inherent limitations associated with a case report hamper the ability to draw any significant conclusions from the results obtained. However the positive results hold value as an indicator for further outcome based studies, more rigid in design while addressing the limitations of previous trials and case observations. To the author's credit, this publication does describe its own limitations.</p> <p>The stringent evaluation of the level of spinal neuro-pathophysiology by means of thermal imaging, does however adequately demonstrate the positive effect of SMT on aberrant autonomic and central nervous function. This effect supports the theorised mechanism of SMT in the resolution of aberrant autonomic nervous function.</p>
CONCLUSION:	<p>The relatively low ranking of the article by the reviewers indicates that this particular study, although useful provides for very limited evidence in terms of the use of manipulation in this particular clinical context, unless other patients were to present in a similar manner to the patient described in this study. Therefore given the complexity of this patient's case, the likelihood that the treatment programme was tailored specifically to the patient and that the outcomes were not very specific can only lead to the conclusion that the study provides limited evidence for the support of manipulation in ameliorating IBS.</p>

Table 4.38: Tabulated feedback data of Article 18: LIDDLE SCALE

AUTHOR(S):		Wagner T; Owen J and Malone E.					
YEAR:		1995					
TITLE:		Irritable bowel syndrome and spinal manipulation: a case report					
CRITERION:			Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage Agreement
1	Are the study participants well-defined in terms of time, place and person?		A	A	A	A	100%
2	What percentage of individuals refused to participate?		n/a	n/a	n/a	n/a	100%
3	Are outcomes measured in a standard, valid and reliable way?		C	B2	C	C	66%
4	Are outcomes measured in the same way for both intervention and control groups?		n/a	n/a	n/a	n/a	100%
5	Are factors other than intervention comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?		n/a	n/a	n/a	n/a	100%
6	What percentage of individuals recruited into the study are not included in the analysis?		n/a	n/a	n/a	n/a	100%
7	Is the analysis by intention to intervene (treat)?		A	A	A	A	100%
8	Are results homogenous between sites?		n/a	n/a	n/a	n/a	100%
9	How well was the study done to minimise bias?		C	B2	C	C	66%
10	Is the overall effect of the study due to the study intervention?		B2	B2	B2	B2	66%
11	Explain if there is any practical/ethical reason why an RCT cannot be done?		A	B1	A	A	66%
	TOTAL SCORE		A: 3 B1: 0 B2: 1 C: 2 I: 0 n/a: 5	A: 2 B1: 1 B2: 3 C: 0 I: 0 n/a: 5	A: 3 B1: 0 B2: 1 C: 2 I: 0 n/a: 5	A: 3* B1: 0 B2: 1 C: 2 I: 0 n/a: 5	
			OVERALL PERCENTAGE AGREEMENT:				87%

Table 4.39 Analysis of Article 18

AUTHOR(S):	Wagner T; Owen J. and Malone E.							
YEAR:	1995							
TITLE:	Irritable bowel syndrome and spinal manipulation: a case report							
STUDY PROPERTIES:								
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors blinded	Control used	Randomisation of participants	Ranking	Total Percentage Agreement
Subjective reporting on any changes in symptomatology was done verbally by the patient.	Two days following the initial spinal manipulation, again one week after the second manipulation, with additional reports on each subsequent visit: twice weekly for three weeks.	The treatment plan was designed as follows: -spinal manipulation applied to indicated levels on a twice weekly basis for a period of three weeks. Maintenance treatment was sought on a monthly basis thereafter.	One 25 year old female.	N/A	None	N/A	A : 3 B1 : 0 B2 : 1 C : 2 I : 0 n/a: 5	87%

LIMITATIONS:	<p>As with all single case reports, this study holds many inherent limitations, which hamper the ability to responsibly advocate spinal manipulative therapy (SMT) as successful in the treatment of IBS to the general population. Specifically for this study, these limitations include, the absence of control measures, the reliance on subjective verbal patient reporting specifically on symptomatology and the lack of naivety of the patient with respect to chiropractic care. These limitations are compounded by the sample size of one patient, which does not allow for the generalisability of the outcomes of this study.</p> <p>Additional concerns lie in the lack of any applied criteria in the diagnosis of IBS. The diagnosis was based on physical examination (to exclude any other evident organic disease), laboratory blood analyses (shown to be unremarkable) and vital statistics (all found to be within normal range). Therefore a diagnosis of IBS as such should be reserved. The statement made by the authors that many chiropractors have had success in treating IBS (forming the basis for this case study) seem an unfounded one, and not referenced in this report. This suggests that the evidence is only anecdotal and that this is an attempt at documenting such a case. If this latter holds true the author is to be congratulated in attempting to document and report such a case.</p>
OUTCOME:	<p>According to the article, the patient reported a complete resolution of her diarrheal symptoms two days after receiving her first chiropractic treatment. This effect was sustained over the duration of the three weeks, and maintained with monthly follow-up treatments.</p>
DISCUSSION:	<p>Even though this case report lacks in methodological rigor and falls prey to the limitations of a case report, the reportedly remarkable effect that SMT had on the patient's diarrheal symptoms, warrants further investigation in this field. Future research, while addressing the flaws of this case report, is certainly indicated.</p>
CONCLUSION:	<p>The evidence provided by this article is at best very limited, given the outcomes of the review provided by the reviewers in Table 4.40. However the outcomes of the case report does warrant further critical investigation in terms of gastro-intestinal symptoms and the effect that SMT has on these symptoms.</p>

4.5 Conclusion

Chapter Four presented the findings of the reviewers and their rating of each of the articles within this systematic review on the treatment of IBS. These review findings reflect the methodological rigour of the study with emphasis on the internal factors which are directly related to the study design, protocol an execution.

The reviewers' outcome was then linked to a qualitative assessment of the article in order to determine the overall evidence that the article provides in terms of the tested intervention for the treatment of IBS. This outcome represents the degree to which the article actively contributes to the evidence within a particular clinical construct. This qualitative assessment was guided by the articles properties, structure, limitations and outcomes, which are not primarily assessed through the scales applied to the respective articles by the reviewers; but nonetheless have an impact on the results obtained in the study. This allows you, the reader, to contextualise the possible reasons for the reviewer ranking of the articles as well as the outcomes of the articles.

However, to meet the outcomes of this study, Chapter Five presents a discussion around each of the treatment options for IBS represented by the articles critiqued in Chapter Four, in order to determine the collective evidence available for the different manual therapy interventions for IBS. This discussion is based on findings produced after the application of Foley's criteria.

CHAPTER 5

DISCUSSION OF RESULTS

5.1 Introduction

The purpose of this chapter is to argue/establish the value of the evidence produced by the studies as reviewed and described in Chapter Four, in order to determine the level of evidence available for each of the non-invasive manual treatment modalities utilised in the treatment of IBS.

5.2 Review of non-invasive manual therapies used in the management of IBS

This review delivered the following studies relating to non-invasive manual therapies employed in the management of IBS:

Table 5.1: Studies evaluated in this systematic review as per intervention type
(alphabetised and arranged in order of study type hierarchy)

INTERVENTION	AUTHOR/YEAR	STUDY TYPE
OSTEOPATHY	<ul style="list-style-type: none"> • Attali T; Bouchoucha M; Benamouzig R. (2013) • Brice C. and Mountford R. (2000) • Florance B.M; Frin G; Dainese R; Nebot-Vivinus M.H; Barjoan E.M; Marjoux S; Laurens J.P; Payrouse J.L; Hebuterne X; Piche T. (2012) 	<ul style="list-style-type: none"> • RCT • RCT • RCT
	<ul style="list-style-type: none"> • Gamber R.G; Shores J.H; Russo D.P; Jimenez C; Rubin B.R. (2002) • Hundscheid H.W.C; Pepels M.J.A.E; Engels L.G.J.B; Loffeld R.J.L.F. (2006) • PicheT;Pishvaie D; Tirouvaziam D; Filippi J; Dainese R; Tonohouhan M; DeGalleani L; Nebot-VivinusM.h; Payrouse J.L. and Hebuterne X. (2014) • Perrin R.N; Edwards J and Hartley P. (1998) • Pizzolorusso G; Turi P; Barlafante G; Cerritelli F; Renzetti C; Cozzolino V; D'Orazio M; Fusilli P, Carinci F. and D'Inecco C. (2011) 	<ul style="list-style-type: none"> • RCT • RCT • RCT • nRCT • nRCT
CHIROPRACTIC	<ul style="list-style-type: none"> • Munton R. (1999) • Amalu W.C. (1998) • Wagner T; Owen J. and Malone E. (1993) 	<ul style="list-style-type: none"> • RCT • C/S • C/S

INTERVENTION	AUTHOR & DATE	STUDY TYPE
YOGA	<ul style="list-style-type: none"> • Kuttner L; Chambers C.T; Hardial J; Israel D.M; Jacobson K; Evans K. (2006) • Taneja I; Deepak K.K; Poojary G; Acharya I.N; Pandey R.M; Sharma M.P. (2004) • Brands M.M.M.G; Purperhart H; Deckers-Kocken J.M. (2011) 	<ul style="list-style-type: none"> • RCT • RCT • nRCT
Traditional Chinese Spinal Orthopedic Manipulation	<ul style="list-style-type: none"> • Xing L; Qu L; Chen H; Gao S. (2013) • Qu L; Xing L; Norman W; Chen H; Gao S. (2012) 	<ul style="list-style-type: none"> • RCT • RCT
MASSAGE	<ul style="list-style-type: none"> • Lamas K; Lindholm L; Stenlund H; Engstrom B; Jacobsson C. (2009) 	<ul style="list-style-type: none"> • RCT
REFLEXOLOGY	<ul style="list-style-type: none"> • Tovey, P. (2001) 	<ul style="list-style-type: none"> • RCT

5.3 Criteria for grading evidence for each of the tested interventions

The studies that were evaluated in this systematic review (see Table 5.1), were individually graded (Chapter Four) based on a review of their methodological rigour. This outcome was assigned according to the outcome of a critique of the respective articles by the researcher, as well as a review of the articles by blinded reviewers (utilising the relevant scales to make a determination as to the level of evidence each article contributes in its own right).

This chapter aims to utilise the criteria as defined by Foley *et al.* (2003), in order to culminate all the evidence for each of the intervention types in order to make a collective determination about the interventions reviewed in this systematic review viz. osteopathy, chiropractic, TCOSM, massage, reflexology and yoga. According to Foley *et al.* (2003), literature considers the following six categories of evidence types:

- The first three categories address the level/quality of the evidence produced.
1. “*Strong*”: where the evidence of the studies within a specific intervention group (e.g. osteopathy or reflexology) is supported by the results of at least *two* RCT’s which achieved at least a “fair or moderate” grading.

2. *“Moderate”*: where the evidence of the studies within a specific intervention group (e.g. osteopathy or reflexology) is supported by the results of *one* RCT which achieved at least a “fair or moderate” grading.
 3. *“Limited”*: where the evidence of the studies within a specific intervention group (e.g. osteopathy or reflexology) is supported by the results of at least *one* non-experimental study (e.g. nRCT).
- The following two categories describe whether or not there are any conflicting results among studies of a specific intervention. These include :
4. *“Consensus”* : which collectively refers to a) consensus could be reached among the reviewers as to whether or not the specific intervention could be effective in the management of IBS or b) the outcome of the specific intervention is consistent among other studies.
 5. *“Conflicting”*: when disparity exists between results of at least two RCT’s. In the case where only one RCT in a group of several RCT’s shows disparity, the results of the majority of the studies is considered the platform from which deduction can be made.
- This final category presents “no evidence”.
6. *“No evidence”*: in the event that either a) a highly graded study reveals that the intervention on trial scores no higher than the placebo, or b) a low grade study produces little to no evidence.

These criteria are based on the levels of evidence employed by the US Agency for Healthcare Policy and Research (Foley *et al.* 2003). By following this method, it was easy to draw conclusions where various studies were found to be in agreement. However, interpretation of individual study results as a collective proved more

challenging when study results conflicted. It is therefore required that the reader(s) be critical in their consumption of the researcher's interpretation.

5.4 Grading of evidence for each intervention

5.4.1 Osteopathy

Table 5.2 OSTEOPATHY

Author(s) / Year:	Study Type & (level of evidence provided per article)	Methodological Ranking:	Collective Level of Evidence per Intervention (<i>Foley Criteria</i>)					
			Strong	Moderate	Limited	Consensus	Conflicting	No Evidence
Attali T; Bouchoucha M; Benamouzig R. (2013)	RCT (moderate)	6/11	X			Consensus		
Brice C. and Mountford R. (2000)	RCT (limited)	6/11						
Florance B.M; Frin G; Dainese R; Nebot-Vivinus M.H; Barjoan E.M; Marjoux S; Laurens J.P; Payrouse J.L; Hebutterne X; Piche T. (2012)	RCT (moderate)	7/11						
Gamber R.G; Shores J.H; Russo D.P; Jimenez C; Rubin B.R. (2002)	RCT (limited)	6/11						
Hundscheid H.W.C; Pepels M.J.A.E; Engels L.G.J.B; Loffeld R.J.L.F. (2006)	RCT (moderate)	7/11						
PicheT;Pishvaie D; Tirouvaziam D; Filippi J; Dainese R; Tonohouhan M; DeGalleani L; Nebot-VivinusM.h; Payrouse J.L. and Hebutterne X. (2014)	RCT (moderate)	7/11						
Perrin R.N; Edwards J and Hartley P. (1998)	nRCT (limited)	4.5/9						
Pizzolorusso G; Turi P; Barlafante G; Cerritelli F; Renzetti C; Cozzolino V; D'Orazio M; Fusilli P, Carinci F. and D'Inecco C. (2011)	nRCT (good)	7/9						

Discussion of Table 5.2

Given the outcomes of these reviews, it would suggest that there is strong evidence [minimum of two RCTs with a fair to moderate rating (Foley *et al.*, 2003)] in favour of osteopathic care being utilised as an *adjunctive* in the treatment of IBS. This latter contextualisation is necessary as many of the articles that provided evidence for osteopathic care did not test osteopathic techniques in isolation (e.g. patients were still able to continue with medication) and often the osteopathic care provided was of a “black box format” where the practitioner applied various techniques required by the patient at different stages within the study.

In addition it should also be noted that the osteopathic techniques were provided for a limited age range of patients, with the strongest studies being for the younger age group. It is therefore suggested that further research consider older population groups in order to more effectively delineate the effect of osteopathic techniques in the presence of concomitant medication use (which was limited in the paediatric and younger age groups). Additionally, future research should also look at delineating specific osteopathic techniques (outside of osteopathic treatment programmes), in order to determine which technique(s) are more effective in which age group / gender, in order for clinical prediction rules to be formalised.

Three studies in the osteopathy study category, were indirectly related to IBS (Gamber *et al.* 2002; Perrin *et al.* 1998 and Pizzolorusso *et al.* 2011). Due consideration is therefore required when reflecting on their individual contribution to the collective evidence in support of osteopathic treatment in the management of IBS related symptoms. Where two RCTs with moderate ratings share outcomes, the collective evidence is considered strong for their outcomes (Foley *et al.* 2003). According to this criteria osteopathy would've presented with a strong level of evidence regardless of these three studies' inclusion.

5.4.2 Chiropractic

Table 5.3: CHIROPRACTIC

Author(s) / Year:	Study Type & (level of evidence provided per article)	Methodological Ranking:	Collective Level of Evidence per Intervention (<i>Foley Criteria</i>)					
			Strong	Moderate	Limited	Consensus	Conflicting	No Evidence
Munton, R. (1999)	RCT (none)	8/11			X	Consensus		
Amalu W.C. (1998)	CS (limited)	A: 2 B1: 1 B2: 2 C: 1 I: 0 na: 5						
Wagner T; Owen J. and Malone E. (1993)	CS (limited)	A: 3 B1: 0 B2: 1 C: 2 I: 0 na: 5						

Discussion of Table 5.3

Given the three articles that were available in terms of chiropractic care for patients with IBS, it is evident that the literature is not only sparse, but limited in terms of evidentiary support for the use of chiropractic care as a modality in the treatment of IBS, whether it be in a treatment programme or as a stand-alone technique.

For chiropractic to be advocated as a viable intervention for IBS patients, the profession needs to produce increased numbers of more rigorous studies to support the initial claims that may be provided by the evidence outlined in Table 5.3. However, due to consideration of specific techniques is needed, much like osteopathy, in order for a more definitive set of treatment interventions to be identified specifically for IBS patients.

5.4.3 Yoga

Table 5.4: YOGA

Author(s) / Year:	Study Type & (level of evidence provided per article)	Methodological Ranking:	Collective Level of Evidence per Intervention (<i>Foley Criteria</i>)					
			Strong	Moderate	Limited	Consensus	Conflicting	No Evidence
Taneja I; Deepak K.K; Poojary G; Acharya I.N; Pandey R.M; Sharma M.P. (2004)	RCT (moderate)	6/11	X			Consensus		
Kuttner L; Chambers C.T; Hardial J; Israel D.M; Jacobson K; Evans K. (2006)	RCT (moderate)	7/11						
Brands M.M.M.G; Purperhart H; Deckers-Kocken J.M. (2011)	nRCT (limited)	5/9						

Discussion of Table 5.4

In terms of yoga providing adjunctive care for patients with IBS, Table 5.4 indicates that there is strong evidence as per Foley *et al.*'s (2003) criteria. Due consideration of the limitations of these studies is required, as they relied on home care practices (e.g. the patient was required to participate in the study while practicing the yoga at home), which were neither supervised nor documented rigorously, the ensuing effects of which is unclear. It is suggested that these studies are repeated in the future with either the consideration of a "yoga school" that patients would be required to attend or at minimum a yoga diary to be kept in order to determine whether the yoga was indeed the active ingredient of change or whether the heightened awareness of IBS related symptomatology within the research study made the patients more considerate of their IBS and thus more conscientious in maintaining an appropriate lifestyle to reduce the impact of the lifestyle on the IBS.

Notwithstanding the above conundrum, it would be reasonable to assume that yoga does provide a direct care pathway for patients with IBS. It is important to determine which yoga postures, activities and / or regimes would be most appropriate for patient

with specific subsets of IBS. This recommendation is based on the fact that patients in the cited studies requested different postures for ease of completing the yoga programme, as some postures caused discomfort or pain.

5.4.4 Traditional Chinese Spinal Orthopedic Manipulation (TCSOM)

Table 5.5: TCSOM

Author(s) / Year:	Study Type & (level of evidence provided per article)	Methodological Ranking:	Collective Level of Evidence per Intervention (<i>Foley Criteria</i>)					
			Strong	Moderate	Limited	Consensus	Conflicting	No Evidence
Qu L; Xing L; Norman W; Chen H; Gao S. (2012)	RCT (moderate)	7/11		X		Consensus		
Xing L; Qu L; Chen H; Gao S. (2013)	RCT (moderate)	7/11						

Discussion of Table 5.5

In terms of the data provided in the literature for TCSOM, the evidence is moderate and in consensus, indicating that the use of TCSOM in the treatment of IBS could be considered as an adjunctive modality. It must be mentioned that the two TCSOM studies under review are exact in method, with the latest (Xing *et al.* 2013) best serving as an affirmation of the results achieved in the first study (Qu *et al.* 2012). It is suggested that the TCSOM professionals produce increased numbers of more rigorous studies to support these initial claims that are provided by the evidence outlined in Table 5.5. In addition, due consideration of treatment programmes versus specific techniques needs to be considered, much like osteopathy and chiropractic care in order for a more definitive set of treatment interventions to be identified specifically for IBS patients. Therefore, future research should delineate specific TCSOM techniques (outside of TCSOM treatment programmes), in order to determine which technique(s) are more effective in which age group / gender, in order for clinical prediction rules to be formalised.

5.4.5 Massage

Table 5.6: MASSAGE

Author(s) / Year:	Study Type & (level of evidence provided per article)	Methodological Ranking:	Collective Level of Evidence per Intervention (<i>Foley Criteria</i>)					
			Strong	Moderate	Limited	Consensus	Conflicting	No Evidence
Lamas K; Lindholm L; Stenlund H; Engstrom B; Jacobsson C. (2009)	RCT (moderate)	7/11			X	Inconclusive		

Discussion of Table 5.6

Given that only one article under review featured massage, it can be suggested that the evidence for the use of massage as an intervention in the treatment of chronic constipation be inconclusive. This highlights the need for additional research with higher methodological rigour and specific outcomes measures that are directed at the changes within the pathogenesis of the condition, so as to improve the measure of clinical efficacy of massage. Caution should be taken to advocate the use of massage to manage constipation symptoms until such further research.

5.4.6 Reflexology

Table 5.7: REFLEXOLOGY

Author(s) / Year:	Study Type & (level of evidence provided per article)	Methodological Ranking:	Collective Level of Evidence per Intervention (<i>Foley Criteria</i>)					
			Strong	Moderate	Limited	Consensus	Conflicting	No Evidence
Tovey P. (2001)	RCT (none)	8/11				Inconclusive		X

Discussion of Table 5.7

The data available for the use of reflexology as a treatment method for patients with IBS is limited with only one study included in this SR. While the methodological rigour of the study was seen as moderate, the results concluded that reflexology does not offer any statistically significant benefit to patients with IBS. This could suggest that the flaws in the study outside of the structural rigour of the study (e.g. type of patients included and / or the number of treatments allowed concurrently during the study), may be responsible for the variance in the responses of the patients. Therefore future studies need to consider larger sample sizes as well as subtypes of IBS patients, within strict criteria, in addition to specifically identified treatment interventions that can be linked directly to clinical improvement in IBS. This would be analogous to the consideration in developing clinical prediction rules for different subsets of IBS patients, noting specific treatment interventions that are effective for specific subtypes. Another deliberation for future studies is to assess the impact of the *therapist* versus that of the actual intervention.

5.5 Collective Evidence as per Intervention

Table 5.8: Level of evidence delivered per intervention reviewed

Conditions:	Level of Evidence					
	Strong	Moderate	Limited	Consensus	Conflicting	No Evidence
Osteopathy	X			X		
Chiropractic			x	X		
Yoga	X			X		
TCSOM	X			X		
Massage			x	Inconclusive		
Reflexology				Inconclusive		X

Discussion of Table 5.8

Given Table 5.8, representing a summary of the review outcomes for each of the non-invasive manual therapies as a collective whole, it would seem that the osteopathy, yoga and TCSOM interventions had the strongest and most consistent outcome for positive benefit in terms of the IBS patients that were enrolled in the studies that contributed to this literature, while chiropractic care and massage therapy only produced limited evidence and reflexology no evidence to support its use in the management of irritable bowel syndrome. The latter two therapies having a second disadvantage in that the outcomes for the studies were inconclusive and suggestive of conflicting outcomes, which weakens the moderate level of evidence that is provided by the actual studies.

5.6 Conclusion of Chapter Five

The testing of manual therapies is a difficult enterprise in that there is a limitation of blinding with regards to the patients (unless they are totally naïve about the intervention) in addition to a limitation in blinding the practitioners treating patients. This requires that the studies consider independent patient screeners, therapists, outcome assessors in order to effectively blind the process in such a manner as to ensure minimal impact on the outcomes of the study.

Multi-therapy approaches observed in some studies under review (where e.g. patients undergoing the intervention were still allowed to continue with medication and / or were treated in a pragmatic style-as determined by the person treating the patient within the study)- detracted from many of the studies' abilities to draw specific conclusions around particular techniques being responsible for certain outcomes. Additionally the clinical presentation of IBS, as outlined by the Rome Criteria and the Manning Criteria, does not account for all the variables that the patient may present with (e.g. chronicity, additional sequelae). As a result, the lack of sample group homogeneity provides for a difficult environment within which to test specific interventions. This requires some deliberation in order for studies to show greater consistency in the application of the criteria, delineation of the sample populations as well as defining specific subsets of the IBS clinical presentation. Without this, the results of the studies reviewed now and in the future may remain ambivalent as the manner in which these subsets of patients respond is different and directly impacts on the overall outcome of the group's results.

The application of defining clinical prediction rules may be necessary in order to better understand the impact of treatments on patients with IBS. Lastly, monitoring the changes of outcomes in patients with IBS seems to be heavily reliant on subjective outcome measures completed by the patient, with few objective measures that can corroborate these findings. This results in the studies being influenced by patient perception, the "observer effect" and the "Hawthorne effect", which makes it more difficult to conclusively state whether the changes in the patient's clinical presentation is

as a result of the intervention, or the perception that the patient has, influencing their lifestyle choices through the period of the study (McCambridge *et al.* 2013).

Notwithstanding the varying levels of evidence across interventions (viz. strong for osteopathy, yoga and TCSOM; limited for chiropractic and massage; and no evidence for reflexology), significantly more research is required in *all* fields addressing the concerns highlighted in this discussion in order for the evidence on non-invasive manual therapy to be improved and better evaluated so that practical recommendations for patients are based on a solid evidence based foundation (Bronfort *et al.* 2010).

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 Introduction

This chapter provides a conclusion to the dissertation and presents recommendations in terms of the study outcomes, for future studies as well as in practical terms for practitioners potentially utilising the interventions reviewed.

6.2 Conclusions

The aim of this study was to identify, analyse and critique the literature (published and grey) in order to state the level and rigour of the current knowledge of the effectiveness of non-invasive manual therapies in the treatment of IBS. To achieve this outcome, a database and hand search for appropriate articles was systematically and methodically completed (as outlined in Chapter Three). These articles were then screened through a process of citation review, abstract review and then article review for inclusion into or exclusion from the study. This process yielded a total of eighteen articles. Seven appointed reviewers (in combination no more than three reviewers per article), were then tasked to review the articles by applying appropriate scales of measurement viz. PEDRO, Newcastle-Ottawa and Liddle scales (Appendices E, G and I respectively). This process was utilised such that each article could be ranked according to the level of rigour which it represented. This was combined with a qualitative analysis of each article respectively in order to determine the level of evidence that the article provided either in support of, or against the use of the intervention in patients with IBS. With the assessment of each of the articles in mind, the majority of the articles (RCTs and nRCTs) ranked in the 'moderate' level of evidence range, with the case studies falling within the 'limited' range.

When the data was further analysed in groups representing the different interventions viz chiropractic care, osteopathic care, traditional Chinese spinal orthopedic manipulation (TCSOM), massage, reflexology and yoga, it was found that

osteopathic care, yoga therapy and TCSOM interventions had the strongest and most consistent outcome for positive benefit in terms of the patients that were enrolled in these studies. Chiropractic care as well as massage therapy presented with only limited evidence in support of their use in the treatment of IBS related symptoms, with no evidence presented in support of reflexology as a viable modality for IBS patients. The need for further research, in all of the above fields, is evident. To expand on the limited pool of existing evidence would strengthen the available literature and allow for improved clinical decision making based on evidence that is of high quality and practical value.

6.3 Recommendations

6.3.1 Recommendations to improve this study

In terms of this study, it is recommended that future systematic reviews improve their outcomes, by ensuring that there is no bias by the sole use of English articles. It is suggested that the translation of articles into English be considered as this has the greatest potential for inclusion of all studies within a particular context and thus into the systematic review. However, this opens the possibility of translation-bias (Scollen and Scollen 1995), which may in turn be detrimental to the study. Another possibility would be to utilise a reviewer group that enables the review of articles from different language sources, yet have their reporting done in English to allow for a common language in which the results are articulated.

Although this study did not have participating reviewers articulate any concerns regarding their interpretation of measurement tools (viz. rating scales), it may be a consideration for future studies to consider a training programme for reviewers to ensure that all members of the research group have the same point of reference.

6.3.2 Recommendations for future studies

In terms of future studies in the IBS domain, it would be important for authors to follow appropriate publication guidelines for the type of study that they wish to publish (e.g. RCTs, nRCTs, cases). This not only makes reviewing these studies easier and more efficient, but it also highlights the rigour to more novice readers. In addition, this improved methodological presentation may improve the rigour of the study as seen by the reader and could result in increasing reviewer agreement, thereby adding further validity and credibility to the study in question and to the domain in which the publication is published (e.g. domain of IBS).

To improve evidence within a certain field like IBS, it is necessary for researchers to consider study types that are likely to provide stronger forms of evidence – therefore a recommendation of RCTs over nRCTs and case series or case studies. This is particularly true in the field of manual therapy, where many studies seem to be pragmatic in nature. Although this is based on the nature of the interventions, attempts should be made to perform RCTs within the guidelines for such studies.

It is further suggested that factors are incorporated into the methodology to make the study structure more rigorous and sound. These factors may include, but not be limited to: using an optimal sample size; determining sample size by means of an *a priori* calculation; considering carefully the inclusion of males, females or both; the use of stringent inclusion and exclusion criteria (e.g. defining the different IBS subsets clearly); thoroughly and systematically documenting all diagnostic / intervention and / or follow-up procedures; allowing for a standardisation of the interventions between participant groups as well as the appropriate use of a control group. A noteworthy consequence of a longer follow-up period is the opportunity to record and report on any possible adverse effects that may take time to manifest.

Guidelines for the use of standardised outcome measures within the domain of IBS are seemingly limited, rendering the need for the development of a core outcome set. Such measures will not only contribute to the rigour of future studies, but will also ensure that the data across these studies are comparable at the level of statistical meta-analysis.

6.3.3 Recommendations for practitioners

With many patients turning to alternative therapy forms, for conditions that are recalcitrant in terms of their response to traditional medical interventions (Drossman, Morris *et al.* 2009; Hussain and Quigley 2006; Kong *et al.* 2005; Koloski *et al.* 2003), it is important for practitioners to have access to high quality literature to guide them in their decision making process, particularly as practitioners are increasingly required to work within an evidence informed model of practice (Bronfort *et al.* 2010). This evidence-informed practice demands that practitioners utilise appropriate and validated tools to consistently and accurately measure their patient progress through the course of their treatment.

Given the conclusions of this study, it is clear that until further research is able to substantiate and/or expand on claims made by the limited evidence currently available, practitioners would be well advised to moderate their recommendation of, or referral to, such treatment interventions as osteopathic care, chiropractic care, TCSOM and yoga therapy in patients that present with IBS. Extra caution should be taken with regards to recommending massage and reflexology therapy in these patients, as the available evidence for these two interventions was found to be inconclusive. This will allow practitioners to avoid the pitfalls of informed consent and dispensing care without the necessary evidence-based support of the literature.

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Appendix A: Search Engines searched

Summons
109 099

Google Scholar
197 000

Proquest
2781

Science Direct
24 077

Ebscohost including sport discus
2 260

Springer Link
0

PubMed /
Medline
10 826

CINAHL
1250

Total : 347 293

When excluding : Books, Chapters in books, Newspaper articles, Documentaries, Opinion papers, Government gazettes, Health care guidelines, unpublished dissertations

The total falls to 13 342

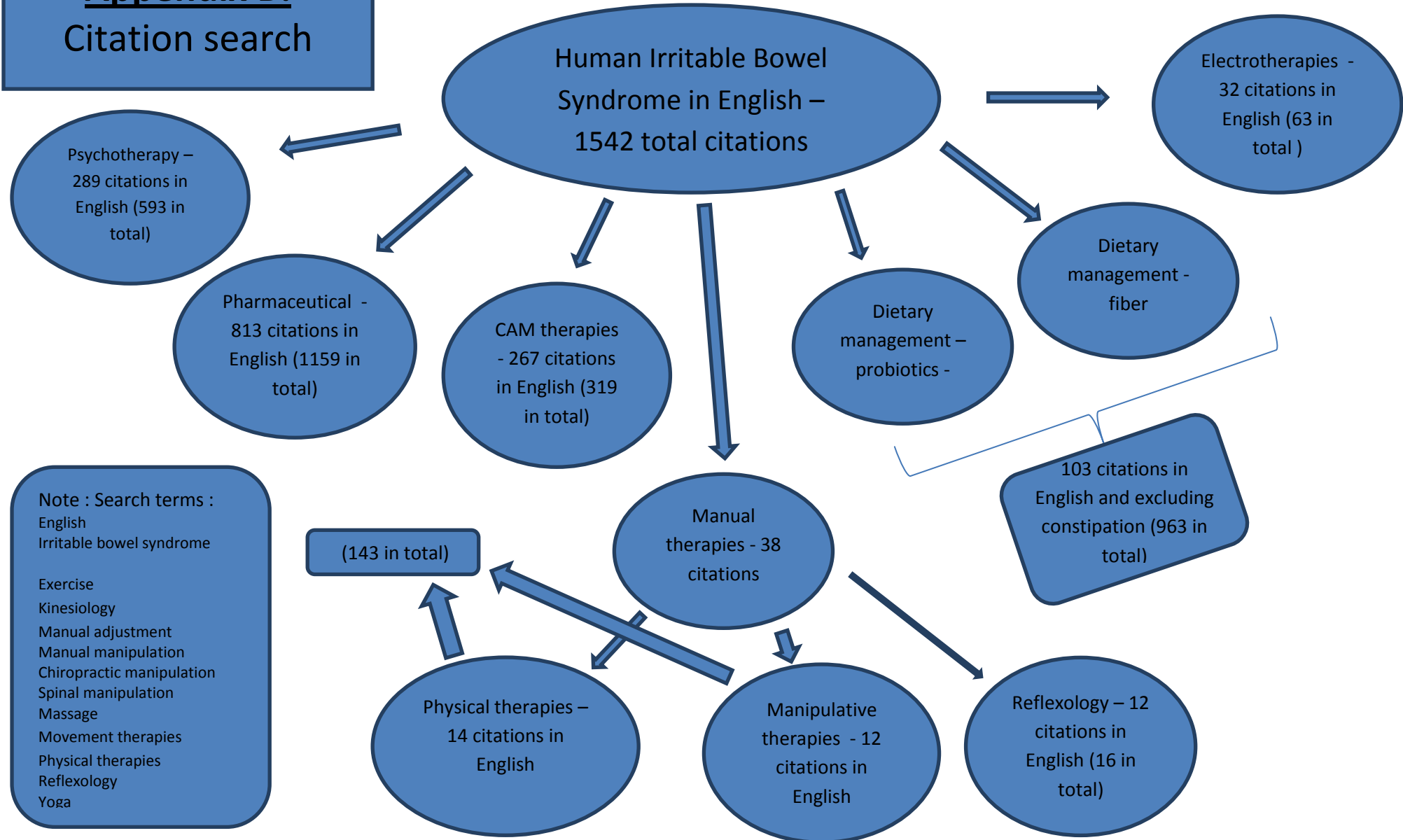
Total : 13 342

When considering : only human studies for irritable bowel syndrome (for all interventions listed below this box) and accounting for any duplicated citations

The total falls to 1542

CAM therapies include : Homoeopathy, Herbal, Phytotherapy, Aromatherapy, Eastern medicines (defined as being non-manual and / or invasive)
Physical Therapies include : Movement therapy, Exercise, Thermotherapy, Yoga, Kinesiology (defined as the application of manual, non-invasive therapy)
Electromodalities include : Ultrasound, TENS, IFC (defined as non-manual and / or invasive)
Psychotherapy, Pharmaceutical, Dietary were defined as non-manual and / or invasive)

Appendix B: Citation search



CAM therapies include : Homoeopathy, Herbal, Phytotherapy, Aromatherapy, Eastern medicines (defined as being non-manual and / or invasive)

Physical Therapies include : Movement therapy, Exercise, Thermotherapy, Yoga, Kinesiology (defined as the application of manual, non-invasive therapy)

Electromodalities include : Ultrasound, TENS, IFC (defined as non-manual and / or invasive)

Psychotherapy, Pharmaceutical, Dietary were defined as non-manual and / or invasive)

Appendix C:
**Full Article review /
hand search**

Manual therapies - 38 citations

Physical therapies
–
14 citations in
English

Manipulative
therapies -
12 citations in
English

Reflexology –
12 citations in
English

Excluded full text :

Physical therapy excluded : 12
Manipulative therapy excluded :0
Reflexology excluded :11

Physical therapies
-
2 met the
inclusion criteria

Manipulative
therapies –
12 met the
inclusion criteria

Reflexology -
1 met the
inclusion criteria

Included due to hand search :

Physical therapy included :1
Manipulative therapy included :2
Reflexology included :0

Final Totals :18
Physical therapy included in this study : 3
Manipulative therapy included in this study: 14
Reflexology included in this study: 1

Appendix D

Reviewer Search

All systematic reviews in regard irritable bowel syndrome where sourced.

All authors where identified and corresponding author addresses where sourced.

All authors with corresponding addresses were then located on the internet and their :

- Qualifications (highest qualification), publications, academic (teaching), clinical (practise) and research experience where noted and tabulated.

The potential reviewers are then contacted electronically asking whether they would consider participation in the systematic review (as proposed in this study), the provisions for participation should the reviewer agree are :

- That the proposal is approved through RHDC and IREC (as appropriate)
- That the reviewer has the time to commit to the process in the timeframe indicated for this proposal

Once the proposal is approved – each reviewer will be sent the MoA (Appendix K) for completion and return to the researcher

Once this has been completed, the reviewers will be tabulated again to ensure that the reviewers are equitably spread in terms of experience and qualifications per study review group

Once the MoA is in place for all reviewers, then the data set for their respective groups will be sent to them electronically (individually) with a timeline extracted from the MoA.

Reviewers will be followed up after 1 weeks to determine whether there are any concerns or problems.

Reviewers will be reminded of their deadline 7 days in advance of the deadline

A letter of appreciation will be sent to all reviewers once all have completed their contribution to the study.

Appendix E:

PEDro Scale: Rating Sheet

The PEDro scale is used for rating the methodological quality of randomised controlled trials. Accessed from <http://www.pedro.org.au>.

For all criteria: Points are only awarded when a criterion is clearly satisfied and reported. Scoring guidelines can be found below.

1. Eligibility criteria were specified	No
	Yes
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	No
	Yes
3. Allocation was concealed	No
	Yes
4. The groups were similar at baseline regarding the most important prognostic indicators	No
	Yes
5. There was blinding of all subjects	No
	Yes
6. There was blinding of all therapists who administered the therapy	No
	Yes
7. There was blinding of all assessors who measured at least one key outcome	No
	yes
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	No
	Yes
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	No
	Yes
10. The results of between-group statistical comparisons are reported for at least one key outcome	No
	Yes
11. The study provides both point measures and measures of variability for at least one key outcome	No
	Yes

Appendix F:

PEDro Scale Explanation

Randomised Controlled Clinical Trial Rating

The PEDro scale is based upon the Delphi list (Delphi list: a criteria list for quality assessment of RCTs for conducting systematic reviews developed by the Delphi consensus. Journal of Clinical Epidemiology, 51(12): 1235-1241). The purpose of the PEDro scale is to determine “internal validity” of a RCT, reflected by criteria 2 – 9. Criterion 1 reflects external validity of the RCT, or simply the applicability of the trial. Criteria 10 – 11 represents whether the RCT statistical information is interpretable.

An additional area in the rating sheet is provided labelled as “where” in order for the page number to be referenced, in the event that there is a disagreement between reviewers this will be used in order to reference where your information was taken from.

The following is an explanation for each individual criterion:

When completing the scale a total of 11 criteria are available. 1 point is awarded for each criterion if the respective criterion is clearly satisfied. When answering yes to a criterion, 1 point is awarded.

Criterion 1	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.
Criterion 2	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	<i>Concealed allocation</i> means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was “off-site”.
Criterion 4	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups’ outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented. 7-11 <i>Key outcomes</i> are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 5	<i>Blinding</i> means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be “blind” if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (e.g., visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 4, 7-11	<i>Key outcomes</i> are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 8	This criterion is only satisfied if the report explicitly states <i>both</i> the number of subjects initially allocated to groups <i>and</i> the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 9	An <i>intention to treat</i> analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 10	A <i>between-group</i> statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a “p” value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence

	interval.
Criterion 11	A <i>point measure</i> is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. <i>Measures of variability</i> include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

Adapted from: *PEDro scale* (online). 1999.

Definition of Intention to treat: Fisher et al., (1990) describes intention to treat as an approach for the analysis of RCTs. This strategy associates patients in the groups they were originally randomly assigned to.

Generally, this is interpreted as including all patients, regardless of whether;

- They fulfilled the inclusion criteria
- Treatment was actually received
- Withdrawal from the trial
- Derivation from the protocol

Clinical effectiveness of an RCT can be overestimated if the intention to treat analysis is not done.

References:

PEDro scale (online). 2011. Available at: www.pedro.org.au (Accessed 06 June 2016).

Adapted from Harrison 2014

PEDro Scale:

Reviewer:	
Article Title:	

Please cross out YES or NO for each criterion:

CRITERION:				REFERENCE PAGE:
1	Eligibility criteria were specified	YES	NO	
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	YES	NO	
3	Allocation was concealed	YES	NO	
4	The groups were similar at baseline regarding the most important prognostic indicators	YES	NO	
5	There was blinding of all subjects	YES	NO	
6	There was blinding of all therapists who administered the therapy	YES	NO	
7	There was blinding of all assessors who measured at least one key outcome	YES	NO	
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	YES	NO	
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	YES	NO	
10	The results of between-group statistical comparisons are reported for at least one key outcome	YES	NO	
11	The study provides both point measures and measures of variability for at least one key outcome	YES	NO	

Adapted from: *PEDro scale* (online). 1999.

Appendix G:

Newcastle – Ottawa Quality Assessment Scale (Case Control Studies)

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

Selection

- 1) Is the case definition adequate?
 - a) Yes, with independent validation *
 - b) Yes, e.g. record linkage or based on self-reports
 - c) No description
- 2) Representativeness of the cases
 - a) Consecutive or obviously representative series of cases *
 - b) Potential for selection biases or not stated
- 3) Selection of Controls
 - a) Community controls *
 - b) Hospital controls
 - c) No description
- 4) Definition of Controls
 - a) No history of disease (endpoint) *
 - b) No description of source

Comparability

- 1) Comparability of cases and controls 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.)

Exposure

- 1) Ascertainment of exposure
 - a) Secure record (e.g. surgical records) *
 - b) Structured interview where blind to case/control status *
 - c) Interview not blinded to case/control status
 - d) Written self-report or medical record only
 - e) No description
 - 2) Same method of ascertainment for cases and controls
 - a) Yes*
 - b) No
 - 3) Non-Response rate
 - a) Same rate for both groups *
 - b) Non respondents described
 - c) Rate different and no designation
- (Adapted from Harrison 2014)

Appendix H:

Newcastle-Ottawa Scale Explanation

Non-Randomised studies

The Newcastle-Ottawa scale is divided into 8 items, that are subdivided into 3 categories; selection, comparability and exposure.

For each of the 8 items, there is a variety of response options; one response (a, b, or c, etc.) is to be chosen, with the exception of the comparability section, where one, two or no response can be chosen.

One star is available to be awarded for each item, excepting comparability, which allows for two stars to be awarded. The maximum amount of stars that a study can be awarded is nine stars.

In the event that a study only contains one group of subjects, comparability cannot be completed, and should be omitted from the scale.

Definition: Ascertainment: To discover with certainty, as through examination or experimentation. (The free dictionary (online))

Reference:

Stang, A. 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*. 25(9): 603-605.

Adapted from Harrison (2014)

Newcastle-Ottawa Quality Assessment Scale:
Non-Randomised Studies

Reviewer:	
Article Title:	

A study can be awarded a maximum of one star for each numbered item within the **selection** and **exposure** categories. A maximum of 2 stars can be awarded for **comparability**.

Please circle the letter you award for each point:

SELECTION:

1. Is the case definition adequate?
 - a. Yes, with independent validation *
 - b. Yes, e.g. record linkage or based on self-reports
 - c. No description
2. Representativeness of the cases
 - a. Consecutive or obviously representative series of cases *
 - b. Potential for selection biases or not stated
3. Selection of controls
 - a. Community controls *
 - b. Hospital controls
 - c. No description
4. Definition of controls
 - a. No history of disease (endpoint) *
 - b. No description of source

COMPARABILITY:

1. Comparability of cohorts on the basis of design or analysis
 - a. Study controls for _____ (Select most important factor) *
 - b. Study controls for **any** additional factor *

EXPOSURE:

1. Ascertainment of exposure
 - a. Secure record (e.g. surgical records) *
 - b. Structured interview where blind to case/control status *
 - c. Interview not blinded to case/control status

- d. Written self-report or medical record only
 - e. No description
2. Same method of ascertainment for cases and controls
- a. Yes *
 - b. No
3. Non-response rate
- a. Same rate for both groups *
 - b. Non respondents described
 - c. Rate different and no designation

Adapted from: Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V. and Losos, M., et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses.*

Appendix I: **Liddle Scale: Case Report/Series**

Reviewer:	
Article Title:	

EVALUATION CRITERIA FOR THE STUDY:	Comments:	Code Option: A, B1, B2, C, or I
1. Are the study participants well-defined in terms of time, place and person?		
2. What percentage of individuals refused to participate?		
3. Are outcomes measured in a standard, valid and reliable way?		
4. Are outcomes measured in the same way for both intervention and control groups?		
5. Are factors other than the intervention e.g. confounding factors, comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?		
6. What percentage of individuals recruited in to the study are not included in the analysis? (loss to follow-up).		
7. Is the analysis by intention to intervene (treat)?		
8. Are results homogeneous between sites? (multicentre/multisite studies only).		
OVERALL ASSESSMENT OF THE STUDY:		
1. How well was the study done to minimise bias? IF coded as B1, B2 or C, what is the likely direction in which bias might affect the study results?		
2. Is the overall effect of the study due to the study intervention?		
3. Explain if there is any practical/ethical reason why an RCT cannot be done.		
4. Include any other comments		

Adapted from: Liddle, J.,Williamson, M., and Irwig, I. 1996. *Method for evaluating research and guideline evidence*. New south Wales Department of Health, Sydney, Australia.

Appendix J :

Liddle Scale Explanation

Case Reports/Series and Observational Studies

Codes for evaluation criteria:

<u>Evaluation criteria are coded according to the extent to which the criteria are fulfilled</u>	<u>Code</u>
Criterion entirely fulfilled	A
Criterion mostly fulfilled	B1
Criterion mostly not fulfilled	B2
Criterion not at all fulfilled	C
Criterion not described adequately to classify as a,b1,b2 or c	I
Criterion not applicable	n/a

Codes for overall assessment of quality of study checklists:

Low risk of bias	A	All or most evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled, the conclusions of the study are thought very unlikely to alter.
Low-moderate risk of bias	B1	Some evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought unlikely to alter.
Moderate to high risk of bias	B2	Some evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought likely to alter.
High risk of bias	C	Few or no evaluation criteria fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought very likely to alter.

Adapted from: Liddle, J., Williamson, M. and Irwig, I. 1996. *Method for evaluating research and guideline evidence*. New South Wales Department of Health, Sydney, Australia.

Liddle Scale: Case Report/Series

Reviewer:			
EVALUATION CRITERIA FOR THE STUDY:			Comments:
Article Title:			
1. Are the study participants well-defined in terms of time, place and person?			
2. What percentage of individuals refused to participate?			
3. Are outcomes measured in a standard, valid and reliable way?			
4. Are outcomes measured in the same way for both intervention and control groups?			
5. Are factors other than the intervention e.g. confounding factors, comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?			
6. What percentage of individuals recruited in to the study are not included in the analysis? (loss to follow-up).			
7. Is the analysis by intention to intervene (treat)?			
8. Are results homogeneous between sites? (multicentre/multisite studies only).			
OVERALL ASSESSMENT OF THE STUDY:			
1. How well was the study done to minimise bias? IF coded as B1, B2 or C, what is the likely direction in which bias might affect the study results?			
2. Is the overall effect of the study due to the study intervention?			
3. Explain if there is any practical/ethical reason why an RCT cannot be done.			
4. Include any other comments			

Adapted from: Liddle, J., Williamson, M., and Irwig, I. 1996. *Method for evaluating research and guideline evidence*. New south Wales Department of Health, Sydney.

Appendix K:

Memorandum of Agreement

Title of Research Study: A systematic review of non-invasive manual therapies in the management of irritable bowel syndrome.

Principle investigators: Ms Nannick Badenhorst (Researcher)

Co-investigators: Dr C. Korporaal (Supervisor)

Brief Introduction and Purpose of the Study:

This study is a systematic review of literature pertaining to the use of non invasive manual therapies in the treatment of irritable bowel syndrome.

Articles were collected electronically via databases by the researcher, the articles included into the study are divided into different study types of those only randomised controlled clinical trials/clinical trials, case reports/series and observational studies are included in this study. The articles will be reviewed by a panel of 7 reviewers using quality assessment rating scales (specific to the study types listed above) and feedback from yourselves as reviewers will be collated and presented in a Masters Dissertation.

Outline of Procedures:

You will receive articles which have been grouped according to study type (RCCT's, case report/series and observational studies) as well as the corresponding scale rating sheet (RCCT's – PEDro scale, Case report/series and observational studies - Newcastle-Ottawa scale, Non-randomised clinical trials – Liddle scale) as well as an explanation sheet for each scale.

You will then be requested to individually read and rate each article according to its respective scale. Rating sheets will be collected by my research supervisor (charmak@dut.ac.za) as I am also a reviewer and therefore cannot access your reviews until I have completed all my reviews. The data will then be collated for analysis. Each reviewer will be expected to review between 7-9 publications within a five week period.

You will be contacted initially with all the documents, a follow up email will be sent about 5 days later to confirm receipt and answer any questions that you, the reviewer, may have. This will be followed at about four weeks with a reminder email regarding the deadline at the end of five weeks.

Confidentiality:

You, as reviewers are requested not to discuss the review or any part of its contents with any of their peers during the review process, as you will not be aware of who the other reviewers are and we wish to ensure that we do not contaminate the results by having peer discussions which may influence outcomes.

Benefits: Publication of the study. Should this study be published, all persons participating in the study will be included in the publication (unless you request to be excluded). Should you as a reviewer wish to be exempt from this or excluded from this, please strike through this paragraph and initial alongside.

Remuneration: An honorarium of R1, 000.00 is awarded to each reviewer in appreciation of their time and dedication to this project.

Contact persons: Please do not hesitate to contact either the supervisor and/or researcher regarding any questions or queries via the following methods:

Dr. Charmaine Korporaal (Supervisor):

Telephone: 031 373 2611

Cell no.: 083 463 3562

E-mail: Charmak@dut.ac.za

Ms Nannick Badenhorst (Researcher)

Cell No.: 084 431 7735

E-mail: nannickbadenhorst@gmail.com

Statement of Agreement to Participate in the Research Study:

I (reviewer's full name),(Identity number/
passport number), have read this document in its entirety and understand its contents.

Where I have had any questions or queries, I have been able to email the researcher (Ms Nannick Badenhorst) and have these explained to me to my satisfaction.

Furthermore, I voluntarily agree to participate in this study as a reviewer.

Reviewer's name:.....

Reviewer's signature:.....Date:.....

Supervisor name:.....

Supervisor signature:.....Date:.....

Researcher name:.....

Researcher signature:.....Date:.....

Adapted from Harrison (2014)

Appendix K : Biopsychosocial Model of IBS (Tanaka *et al.* 2011)

