Adverse events in manual therapy: a systematic review.

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Executive Summary

Background

Under the terms of the Osteopaths Act 1993, the General Osteopathic Council (GOsC) has a statutory duty to protect the public by regulating and developing the osteopathic profession in the United Kingdom. Under the standards of osteopathic practice, osteopaths are required to obtain informed consent to administer treatment to their patients, which infers that an assessment of risk has been made before any clinical decisions are made. High quality summary data about the risks of manual treatments used by osteopaths are not available.

Method

We conducted a systematic review of published literature to investigate the risks associated with manual therapy. The searches were carried out during March 2008.

Results

We identified 60 articles that contained original data about adverse events following manual therapy. Seventeen were systematic and literature reviews; nine were prospective cohort studies the remainder were either: surveys, non prospective cohort studies or case series. We extracted data about risk, incidence, prevalence or nature and type of adverse events. A further 30 randomised controlled trials (RCTs) that reported adverse events as a secondary outcome measure were reviewed.

Thirty-three of the 60 studies were funded by / or conducted by chiropractors, 13 by neurologists and / or medics, 8 by physiotherapist or physical therapists and 6 by academics. None were conducted by Osteopaths. One prospective cohort study and two RCTs included Osteopaths. Nearly all studies investigated the use of spinal manipulation.

Using data from the cohort studies and RCTs, mild adverse events post treatment affect around 40–50% of patients. Major adverse events such as death, vascular insults and major neurological incapacity were very rare. The reported incidence of major cerebrovascular insults, incidents or accidents following cervical manipulation ranged from 1: 120,000 and 1: 1,666,666, (median 1: 1,000,000, excluding extreme outliers). One study reported the incidence of lumbar disc herniations following manipulation as, 1:38,013 lumbar manipulations. Incidence for cauda equina syndrome was reported in two studies, data ranged from <1: 3.7 million to 1:100 million lumbar manipulations.

Most adverse events occurred within 24 hours of treatment (mean 79%, range 63-92%). Most mild

to moderate adverse events, such as muscle soreness, aching and headache resolve within 24 hours (mean 67%, range 55-83%).

In the RCTs, the rate of adverse events in the manual therapy trial arms, were similar to those in the control arms. For RCTs comparing manual therapy with pharmaceutical agents, adverse events were significantly less likely within manual therapy treatment groups.

Being female and patient's first visit, are likely risk factors for reporting adverse events.

Risk factors most closely associated with major adverse events, occurring after manual therapy are unusual neck pain/stiffness, having an upper cervical manipulation, seeing a clinician in the preceding weeks (indicating patient concern about their condition rather than causality).

Conclusions

The reporting and description of adverse events is generally poor and better reporting is required in future studies. Most published data are about manipulation performed by chiropractors. Major adverse events and death are rare as a direct consequence of manual therapy, however, minor adverse events are common in those receiving manual therapy. Although serious adverse events are rare the manual therapist should proceed with caution and avoid cervical manipulation when dealing with patients presenting for treatment of neck pain and stiffness who additionally have, cardiovascular insufficiency, history of recent trauma and unusual headaches. Patients should be advised of the small potential risk of serious of adverse events, prior to manipulation of the cervical spine.

Glossary of terms

AE	adverse event
CAD	cervical artery dissection
CAM	complementary and alternative medicine
CI	confidence interval
CSMT	cervical spinal manipulation treatment
CVA	cerebrovascular accident*
CVI	cerebrovascular incident or insult*
GP	general practitioner
ICAD	internal carotid artery dissection
Inc.	incidence
LBP	low back pain
MT	manual therapy
N&T	nature and type
NSAID	non steroidal anti-inflammatory medication
OR	odds ratio
PCP	primary care physician
Prev.	prevalence
RR	relative risk
SM	spinal manipulation
SMT	spinal manipulative treatment
SR	systematic review
VAD	vertebral artery dissection
VBA	vertebrobasilar accident **
VBI	vertebrobasilar incident **

*These terms are used interchangeably throughout the text to mean: an abnormal condition of the brain characterized by occlusion by an embolus, thrombus, or cerebrovascular hemorrhage or vasospasm, resulting in ischemia of the brain tissues normally perfused by the damaged vessels (Mosby's medical Dictionary 2009)

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1. Background

Osteopathy as a profession is defined and regulated by statute. Individual osteopaths are required to act in accordance within professional guidelines and are subject to the jurisdiction of the law wherever they practice. Under the terms of the Osteopaths Act 1993 (Osteopaths Act HMSO 1993) the General Osteopathic Council (GOsC) has the statutory duty to protect the public by regulating and developing the osteopathic profession. The GOsC *Code of Practice for osteopaths* (current vers: General Osteopathic Council *Code of Practice for osteopaths*, May 2005) forms an essential element in the discharge of that duty. The Code lays down guidance which regulates the standards of conduct and practice expected of osteopaths, the principles of which can be generalised to a wide range of professional situations. Osteopaths are required to make the welfare of their patients their first concern, respect the rights of patients to be fully involved in decisions about their own care, justify public trust and confidence and maintain and protect patient information (General Osteopathic Council *Code of Practice for osteopaths*, 2005).

Within this framework the acknowledgement and respect of individual patient human rights, dignity and autonomy is paramount, and central to these fundamental principals is the doctrine of patient consent. Clause 23 of the Code of Practice states:

'*Your patients have a right to determine what happens to them and consent is their agreement for you to provide the care that you propose. Obtaining consent is a fundamental part of your practice and a legal requirement. If you examine or treat a patient without first obtaining consent you may face criminal and civil as well as GOsC proceedings* (General Osteopathic Council *Code of Practice for osteopaths*, 2005, p.6).

Without consent, examination or treatment could be considered as an assault, negligent practice or a breach of the patient's human rights. However consent is seen as more than just assent or mere compliance. Consent is formulated as a genuine ongoing negotiated participative agreement to receive examination and or treatment. Respect for patient autonomy requires that patients are taken to consent if they are aware of all the relevant and necessary information to make an informed decision. Informed consent is dependent on the absence of impairments or disturbance of mental functioning that could inhibit understanding and therefore responsibility, the provision of information and the absence of duress (General Osteopathic Council *Code of Practice for osteopaths*, 2005).

Clause 24 of the Code of Practice states that:

'Before you examine or treat patients you must obtain their consent. To be valid, consent must be specific, informed and given by the patient or in the case of children who are not competent to consent for themselves, by a parent or guardian. "Specific" means that the patient consents to each distinct procedure and "informed" means that a full explanation has been given in line with clauses 19, 20 and 21'. (General Osteopathic Council *Code of Practice for osteopaths*, 2005, p.6.)

Clause 19 emphasises the necessity for ensuring each patient has realistic expectations while clause 21 mandates the osteopathic practitioner to use his or her professional judgement to assess which information is most appropriate. Clause 20 explicitly states that:

'*You should not only explain the usual inherent risks associated with the particular treatment but also any low risks of seriously debilitating outcomes.'* (General Osteopathic Council *Code of Practice for osteopaths*, 2005, p.6).

The practising osteopath is obliged by the terms of the Code of Practice to be aware of and communicate the nature and purpose of the proposed treatment, the possible risks of treatment, potential complications, the balance of arguments for treatment as opposed to no treatment, the likely outcomes and possible side effects. The imperative to obtain informed consent obliges the practising osteopath to ensure that these issues are communicated in a manner that ensures that they are unambiguous and clear to each and every patient.

Informed consent depends on being able to tell patients of the likely risks and benefits of the treatment interventions proposed. Understanding adverse events is an essential pre-requisite to defining and determining their incidence. At present there are no accepted definitions of minor or major adverse events following osteopathic interventions or other forms of manual therapy treatment, nor are there accurate data about the incidence of these adverse events.

The existing published research in this complex area has been dominated by the neurological, chiropractic and physiotherapy professions. A number of systematic reviews and narrative reviews have been written but most are in a form that is often inappropriate to osteopathic practitioners and communities. Adverse event data is often 'buried' in other results or findings and therefore not always readily accessible. There is a need to synthesise adverse event data and research findings to inform osteopathic clinical practice.

In this systematic review we focus on summarising relevant literature in relation to risk and manual therapies. The introduction to the report gives the reader an overview of the current issues in the area of adverse event reporting, and a conceptual and historical perspective of adverse event reporting in complementary and alternative medicine. We discuss the problems involved in defining adverse events and the methodological issues that surround researching this topic. Additionally we provide a summary of the patho-physiological processes that can occur in the cervical area, that underpin the serious consequences that adverse events can incur. Following this we describe the methodological approach we used to conduct this study and our results. Finally we present a discussion of our findings, indicate areas where there is a need for future research and make recommendations for the future.

2. Introduction

2.1 Overview of adverse events

The use of Complementary and Alternative Medicine (CAM) is increasing (Harris and Rees 2000, World Health Organisation 2000). Although health professionals have an ethical and legal obligation to provide information and gain patient consent, recent research suggests that the provision of reliable information and the practice of gaining informed patient consent in CAM is lacking (Monaco and Smith 2002, Caspi and Holexa 2005). Given the increase in the popularity of complementary medicine, the apparent lack of informed consent and the potential medico legal implications, it is crucial that more evidence is available to inform clinicians and patients.

There is an abundance of reports concerning manual interventions that appear to have done more harm than good (Ernst 2007, Stevinson et al. 2001). Reported adverse outcomes encompass a wide range of phenomena ranging from conditions such as cerebrovascular accident, disc rupture, radiculopathy, myelopathy, cauda equina syndrome and rib fracture, to patient reports of transient headache, stiffness, soreness, depression, radiating pain, sweating etc. Adverse outcomes have been classified under a wide range of categories including 'unpleasant reactions', 'side effects' or 'adverse reactions'. According to accepted international clinical trial terminology the established term for these phenomena is "adverse events". An adverse event may be characterised as any unfavourable and/or unintended sign, symptom or disease that is associated with the use of a therapeutic intervention. However, much of the published data consists of case studies or case series that are characterised by heterogeneity and methodological ambiguity. These provide little reliable information regarding causation or risk (Haneline et al. 2003, Ernst 2001, Ernst 2007, Stevinson et al. 2001, Haldeman and Kohlbeck 1999, Smith et al. 2003).

The "gold standard" in empirical clinical research is the randomised controlled trial (RCT). In an attempt to make the quality of reporting in RCTs more robust, the CONSORT (Consolidated Standards of Reporting Trials) Statement (Begg and Cho et al.1996) has been widely applauded. However, as the CONSORT statement was primarily concerned with the reporting of efficacy it included only one check list item that specifically addressed safety (Ionnidis and Evans et al. 2004). The quality of adverse event reporting in RCTs related to manual therapy is commonly inadequate (Ernst 1999, Cawley 1997). In May 2003 members of the CONSORT group met to address these issues and have produced 10 new recommendations with accompanying examples to emphasise

specific harms-related issues (Better Reporting of Harms in Randomised Trials: An Extension of the CONSORT Statement) (Ioannidis and Evans et al. 2004). Contained within the glossary of this statement is a concise review of current terminology:

- *'Adverse events'*: defined as side effects that are harmful. However the use of the term interchangeably with side effects is criticised as it blurs the crucial issue of causality. The use of the term "adverse event" is advocated to describe harmful events that occur during a clinical trial.
- *'Adverse reaction and adverse drug reaction'*: these terms are reserved for events where causality to the tested intervention is well established (Ionnidis and Evans et al. 2004 p. 782).
- *'Harms'*: defined as '*the totality of possible adverse consequences of an intervention or therapy: they are the direct opposite of benefits against which they must be compared'* (Ionnidis and Evans et al. 2004 p.782).
- *'Safety'*: defined as '*Substantive evidence of an absence of harm. The term is often misused when there is simply absence of evidence of harm*' (Ionnidis and Evans et al. 2004 p.782).
- *'Serious adverse events'*: '*During clinical investigations, adverse events may occur which if suspected to be medicinal product related (adverse drug reactions) might be significant enough to lead to important changes in the way the medicinal product is developed (e.g. change in dose, population, monitoring consent forms). This is particularly true for reactions which in their most severe forms threaten life or function'* (Ionnidis and Evans et al. 2004 p.782).
- *'Side effects'*: defined as '*unintended*' drug effects. The term however does not necessarily imply harm, as some side effects may be beneficial. Furthermore, it tends to understate the importance of harms because '*side*' may be perceived as denoting secondary importance' (Ionnidis and Evans et al. 2004 p. 782).

The collection, classification and analysis of adverse event and harm-related issues linked to the therapeutic administration of medicines has been a principal concern of the pharmaceutical industry for many years and has been the subject of intense national and international scrutiny and regulation (World Health Organisation www.who.int/en, Commission on Human Medicines www.mhra.gov.uk, United States Food and Drug Administration www.fda.gov, Institute for Safe Medication Practices www.ismp.org, Adverse Drug Reactions Advisory Committee www.tga.gov.au/adr/adrac).

Both national and international regulatory bodies and the multinational pharmaceutical industry are making considerable and ongoing efforts to differentiate the concept of an "adverse event". An understanding of these efforts is extremely important for anyone concerned with the study of harms in manual therapy. However the pharmaceutical industry has evolved and operates within a completely different historical, philosophical, cultural, institutional, medico legal and clinical context to that of CAM and, although relevant, many of these insights may not be directly applicable to practising osteopaths. It should also be noted that RCTs are not the ideal study design to identify adverse events and particularly uncommon adverse events.

2.2 CAM and adverse events: a conceptual and historical perspective

Defining adverse events in manual therapy is difficult as they occur in many guises, contexts and settings. They range in severity and impact, and patient and practitioner views can differ. To analyse the prevalence, incidence and risk there is a need for a pragmatic definition of adverse events applicable to manual therapy. The perception of an adverse event or reaction may differ between individual clinicians, between clinicians and patients and may also vary depending on the expectations of either party.

Within mainstream medicine there is ongoing consideration of the definition of adverse events, the most appropriate methods of data collection and analysis and the clinical interpretation of results. Within CAM this consideration is less formalized but produces intense debate. Some schools of thought assert that the uniqueness of osteopathy is not merely the provision of an alternative treatment modality but a radically different diagnostic model. It is argued that to ignore the traditional constitutional osteopathic perspective is to merely present patients with a fundamentally damaging "alternative palliation" that encourages the creation and maintenance of chronic and degenerative conditions and terminal disease. Inflammation, fever, vomiting and other signs and symptoms are seen as 'cleansing crises', fundamentally positive reactions to constitutional osteopathic treatment that addresses the 'toxic states' that underpin disease (Beardmore 2008). Some within chiropractic have asserted that the debate around cervical "adjustments" and the potential risk of vertebrobasilar artery dissection has become increasingly more emotional and political than scientific and evidence-based (Chestnut 2004).

CAM by definition does not subscribe to the tenets of conventional allopathic medicine. The controversies around the hotly debated and contentious term "adverse event" polarises opinion

because it appears to crystallize several fundamental questions concerning the nature of health and healing and the role of the therapist in these processes. These core issues lie at the heart of the identity and autonomy of the various CAM disciplines and the attendant philosophical foundations on which they are based. Perhaps crucially the debates concerning adverse events encapsulate and highlight the issues surrounding how the various complementary therapies can retain their distinct identities, honour their varied and valuable heritages and preserve their traditional wide scope of practice while operating in the 21st Century.

The contemporary medicalised, state-sponsored healthcare environment dominated by national and supranational political, economic and ideological forces is far removed from the 19th Century healthcare environment conditions in which Osteopathy and Chiropractic and some other complementary disciplines were founded. The response made by CAM to the insistent, sometimes contradictory challenges and opportunities provided by the trends towards increasing central regulation, the enhancement of patient autonomy and choice and the movement towards evidence-based medicine, among others, may not only define and shape CAM professions but also determine their very existence as autonomous therapeutic disciplines within contemporary healthcare.

Alternative formulations of healing crises and healing reactions are rooted within a very different philosophical concept of the state and process of human health and well-being from that of conventional allopathic medicine. Within the Naturopathic "Nature Care School" a distinction is made between "disease crises" and "healing crises" (Lindlahr 1926). Hering's Law of Cure (Hering 2006) is a key tenet of Homeopathic Medicine and maintains that a temporary exacerbation of symptoms is a necessary component of bodily cleansing. The Jerisch-Herxeimer reaction (www.tbyil.com/herxeimer.htm) was first observed in antibiotic therapy for neurosyphlis and is considered to be an exaggerated immune reaction generated by the body's inability to expel liberated toxins fast enough.

The diverse philosophical heritage of CAM may, through a positive engagement with the debate surrounding adverse events provide an opportunity for a fruitful dialogue with some medical practitioners who, in the past, have expressed concern that a serious 'indirect' adverse event of CAM is, in fact, interference with effective allopathic care (Abbot and Hill et al.1999).

The strength of the debate that surrounds these issues is testament to the strength of the beliefs and the deep-seated traditions that underpin CAM. A proactive and positive response by CAM to the

debate surrounding ‘adverse events’ may create an unprecedented opportunity for CAM to make, through its diversity, tradition and distinct philosophy, a unique contribution to an important debate in contemporary healthcare.

2.3 Defining adverse events within current manual therapy literature

Published descriptive evidence in the form of case studies demonstrating that manual therapy may be related to serious adverse events began in 1907 with the report of a fracture and dislocation of the Atlas as a complication following cervical manipulation (Roberts 1907). In 1934 the Journal of the American Medical Association reported on a malpractice suit resulting from a fatality after chiropractic treatment for headache (Foster vs Thornton 1934). Since then there have been several reviews of published cases of neurovascular complications arising from cervical manipulative therapy (Leboeuf Yde and Hennius et al. 1997, Terret 1987). In 1999 a review of the literature between 1925–1997, in all languages, reported on 177 such cases (Di Fabio 1999).

Because of the poor quality of evidence within these case studies, there is now a discernable move towards more rigorous research and a clearer definition of adverse events within the manual therapy literature. Attempts to describe and categorise adverse events resulting from spinal manipulative therapy have been apparent since the 1970s. In 1971, Livingstone (Livingstone 1971) proposed an adverse event classification scheme. ‘Accidents’ were considered to be serious permanent impairments including fatalities, ‘Incidents’ were consequences of spinal manipulative therapy evident through their extended duration and or seriousness, ‘Reactions’ were slight and of short duration and ‘Indirect complications’ were caused by delayed diagnosis and inappropriate treatment (Livingstone 1971). In 1994, Grieve differentiated between interventions that produced additional distress and inconvenience to patients for 2/3 weeks or more without improving the presenting complaint and those that produced reversible peripheral radicular symptoms/deficits necessitating possible operative decompression. He further differentiated between interventions that produced central nervous system deficits including cauda equina syndrome, myelopathy and stroke that required urgent hospitalisation and caused potential permanent disability from those that caused death (Palastanga and Boyling eds. 1994).

In the 1990s a number of studies were published that reported a range of descriptive data that represented a considerable advance on definitions produced by the previously available case studies (Leboeuf-Yde et al 1997, Rivett and Milburn 1997, Stenstad et al. 1996, Leboeuf-Yde et al. 1997).

However, these studies used a relatively ill defined and undifferentiated definition of adverse events. For example in a prospective clinic-based survey designed to study the frequency and characteristics of "unpleasant side effects" (Leboeuf-Yde et al 1997) after spinal manipulation information was collected from new chiropractic patients through structured interviews. There was little consideration of the concept of adverse events beyond patient reported signs and symptoms and reports of difficulties with daily activities. Data on the number, type, onset and duration and severity was collected and patients were asked to grade the severity of the discomfort experienced on a 4 point scale. In this essentially descriptive study a distinction is made between "common" and "uncommon reactions" on the basis of the frequency of occurrence (Leboeuf-Yde 1997).

Later studies use more precise definitions. Malone (2002) defines an 'adverse effect' as any detrimental result of the treatment, an 'adverse reaction' is defined as a slight or clinically insignificant short-lived symptom and an 'adverse incident' is defined as an unexpected event resulting in serious impairment injury or fatality (Malone et al. 2002).

The issues of temporality, causation and association are becoming increasingly recognised. Some studies explicitly include the aggravation of existing symptoms as adverse events (Barret and Breen 2000, Cagnie 2005, Thiel et al. 2007). However, in a study of the neurologic complications of chiropractic manipulation these were explicitly excluded:

'*The respondents were asked to report only cases in which the onset of neurologic symptoms or signs was within 24 hours of the chiropractic manipulation and was considered to be a complication of the procedure*'(Lee et al. 1995).

In a study of non-vascular complications of spinal manipulation, cases were only included if the quality of patient symptoms had significantly worsened during treatment, for example, if back pain progressed to radiculopathy or radiculopathy progressed to cauda equina syndrome. Cases were not admitted if only the quantitative severity of the symptoms had worsened. Moreover, patients who suffered neurological deterioration weeks or even days after treatment were excluded on the basis that these exacerbations may have represented the natural history of the condition (Oppenheim et al. 2005).

When detrimental, within-treatment variations in discomfort, pain or movement occur post-treatment, methodological issues arise when considering how, when and if these variations should be termed 'adverse events'. Recent studies consider the nature of adverse events and explicitly state

how they are operationalised. For example, in a prospective, multi-centre cohort study that investigated the predictors for adverse events following chiropractic care for neck pain (Rubinstein 2007), a hierarchy of adverse events is proposed. An 'adverse event' is defined as either a new related complaint or a worsening of the presenting symptoms or an existing complaint by more than 30% (based on an 11 point numerical rating scale). 'Intense adverse events' are defined as any adverse event that scored more than 8 on an 11 point scale. 'Serious adverse events' are considered to be events resulting in death, life-threatening situations or necessitating admission to hospital or causing temporary or permanent disability (Rubinstein et al. 2007). In another study on the frequency and clinical predictors of adverse reactions to chiropractic care of patients with neck pain patients were asked to rate the amount of discomfort experienced after treatment on a six point adverse events topology using an 11 point numerical rating scale ranging from 'no discomfort' (0) to 'unbearable discomfort' (10). The onset and duration of symptoms were recorded in four time bands ranging from less than 10 minutes to more than 24 hours (Hurwitz et al. 2005).

Adverse events do not occur in a vacuum. Adverse events and the perception of adverse events are influenced by a wide range of factors that impact on the wider subtle individual and unique therapeutic relationship between each patient and practitioner. Adverse events are becoming increasingly recognised as patient-specific occurrences intimately linked to a variety of individual psychological and socio demographic variables. These complexities and the methodological challenges associated with them are increasingly being addressed in the contemporary literature. Rubinstein attempts to correlate patient work status and patient expectations, fear or apprehension about their treatment with both positive clinical outcomes and adverse events in those treated by chiropractors for neck pain (Rubinstein et al. 2007, Rubinstein et al. 2008). Hurwitz suggests that patients who experience adverse events may be less satisfied with their care, perceive less improvement in neck symptoms, and have more pain and disability at follow-up (Hurwitz et al. 2004).

Within the developing manual therapy literature an increasingly explicit and differentiated concept of adverse events is emerging. In the future, more rigorous and standardised methods may allow for greater use of meta-analyses and statistical pooling of results across various trials and a wider range of data. There are also increasing attempts to face the methodological challenges posed by pragmatic multi-modal forms of treatment and the necessity to consider confounding variables such as socio-demographic variables and the unique individual patient–therapist interaction.

2.4 Methodological issues in adverse events and manual therapy

In addition to defining adverse events and considering causality there other methodological issues surrounding research in this field.

Data collection

The instruments used for collecting data about adverse events are critical elements in study design. 'Active surveillance' of designated specific adverse events in structured questionnaires or interviews produces very different results from 'passive surveillance' where study participants spontaneously report on their own initiative. The declaration of the possibility of adverse events in patient consent forms may constitute "priming" and skew responses (Myers and Cairns 1987, Ioannidis 2006).

Physiology vs psychology

The therapeutic relationship between patient and therapist is complex and some studies have asserted that reactions to treatment may be either physiological or psychological. Physiological reactions are those that appear to be related to the unique patient-specific tissue reaction to the application of defined manual techniques applied by the practitioner. Psychological reactions are those that occur within the therapeutic relationship as a result of non-specific interactions involving the nuances of the individually negotiated voluntary contract between patient and therapist (Leboeuf-Yde et al. 1996).

Recent research on adverse events is attempting to explore the links between issues such as co-morbidities, work status, duration of disability, educational status and psychological profile and their possible relationships with patient perceptions of adverse events and resultant therapeutic outcomes (Hurwitz et al. 2004, Rubinstein et al. 2008). However the current evidence is contradictory. In a study of neck pain it was found that patients who experienced adverse events were less satisfied with their care, perceived less improvement in their symptoms and had more pain and functional loss at follow up (Hurwitz et al. 2004). By contrast, in studies of patients with low back pain whose treatment included spinal manipulation some categories of "common reactions" were not found to be barriers to positive therapeutic outcomes (Axen et al. 2002). Further research is necessary in this important area.

Comparison with other risk

Conventional medical treatment is not without risk. In a recent study comparing the surgical and

non-surgical treatment of chronic low back pain it was found that 24% of the surgical group had complications almost half of which were considered major (Fritzell et al. 2001). In a study of neck pain the evidence suggested that cervical manipulative therapy, although no more effective than non-steroidal anti-inflammatory drugs (NSAIDs), could be considered safer, possibly by a factor of several hundred times (Dabbs and Lauretti 2006). However, these findings have been questioned on the basis that while NSAID prescription is subject to systematic post-marketing surveillance there are no such procedures for spinal manipulative therapy. Furthermore, the comparison of incidence figures based on a single spinal manipulation compared to a prolonged course of medication may be considered misleading (Stevinson et al. 2001, Ernst and Canter 2006).

Temporality and Causation

The difficulties of ascribing causation on the basis of evidence from uncontrolled case series or case studies are well recognised (Haldeman and Kohlbeck 1999, Smith et al. 2003). Those attempting to ascribe a causal relationship between the appearance of an adverse event and a putatively related therapeutic intervention on the basis of temporality alone face formidable philosophical problems. It has been asserted that the temporal juxtaposition of events may indicate association but cannot in itself satisfy the requirements demanded by the concept of causality (Bradford-Hill 1965).

There are many conceptual and methodological issues surrounding any definition of adverse events that include the exacerbation of existing symptoms. How can we separate symptoms that may have occurred due to the natural history of the presenting condition from those allegedly "caused" by a therapeutic intervention? Similarly there are difficulties in ascribing causation to the latent or long-term manifestation of symptoms that may appear days, weeks or months after a treatment intervention. This begs the question of what may be considered an adequate or appropriate follow-up period in studies of adverse events in manual therapy

Extrinsic factors affecting patient wellbeing may also be involved in the perception or occurrence of an adverse event and possibly independent from the patient/therapist interaction. Non-treatment related adverse events may occur due to incidents that are associated with poor diagnosis, the clinical environment or equipment used to deliver care rather than the practitioner-administered manual techniques themselves (Anderson-Peacock et al. 2005, Thiel and Bolton 2006).

In an attempt to clarify some of these issues without entering into the 'murky waters' of philosophical discourse it has been suggested that a useful approach may be to consider the evident levels of association as an indicator of potential causality (Bradford-Hill 1965).

Association may be considered increasingly likely if the following criteria are satisfied:

1. Strength: That is the association has a high frequency.
2. Consistency: The high frequency is observed across diverse populations.
3. Specificity: The prevalence of the association is high in those experiencing the intervention compared to those who do not.
4. Temporality: Association may be clearer if there is a close temporal relationship.
5. Biological gradient: A positive biological gradient may be seen as a high incidence rate.
6. Plausibility: The existence of a credible mechanism linking the two events.
7. Coherence: The opposite of plausibility i.e. that the proposed linkage does not conflict with generally verifiable facts.
8. Experiment: Is there experimental evidence?
9. Analogy: Are there credible analogies that may allow the acceptance of lower levels of evidence.

(Reproduced from Bradford-Hill 1965)

Heterogeneity of research

The literature regarding adverse events in manual therapy is characterised by heterogeneity. Patients are often selected for studies using convenience samples with a wide variety of presentations and medical histories. Manual therapy interventions are frequently multi-factorial in that they involve a variety of techniques such as soft tissue and myofascial work, muscle energy techniques, active and passive stretching, articulation and high velocity low amplitude thrusts. In the absence of consistent definitions of adverse events, inadequate and unsystematic reporting, lack of sub-group analyses, and methodological difficulties that prohibit meaningful statistical pooling or meta analyses, the interpretation of the existing data is problematic (Mior 2001, Lisi et al. 2005).

Due to a lack of systematic data collection and the paucity of prospective cohort studies the incidence and prevalence of "minor" transient adverse events is likely to be under reported (Vick et al 1996). Similarly the use of data collected primarily from manual therapists themselves may lead to both response and reporting bias. The recall bias apparent in retrospective case series and case reports may result in the overemphasis of memorable, more severe events, and the use of retrospective hospital and institutional data may inflate prevalence figures by multiple counting (Oppenheim 2005). In particular it was noted in a study of cerebrovascular accidents after spinal manipulation, that the evident rarity of events means that even minor variations in the number of cases or the circumstances surrounding such cases can greatly affect interpretation (Leboeuf-Yde et al. 1996).

3. Physiological theories for adverse events occurring in association with the cervical spine.

Neurovascular signs and symptoms relating to the cervical spine may be due to ischaemia of the neural tissue supplied by the vertebrobasilar arterial system. These vascular structures provide approximately 10-20% of the blood supply to the brain and through various branches supply many life-preserving neural structures including the brain stem, cerebellum, spinal cord and the cranial nerves (Bannister (ed) et al 1995).

Approximately 60% of cervical rotation occurs at the atlanto-axial joint (Terret 1987) and it is here that the third segment of the vertebral artery proceeds in a potentially vulnerable course before it enters the foramen magnum. It is the third segment of the vertebral artery that has been the focus of studies investigating the potential biomechanical and pathophysiological processes involved in the genesis of adverse events putatively caused by cervical spinal manipulative therapy (Cagnie et al. 2004, Haneline and Lewkovich 2005, Kerry et al. 2008).

The precise mechanisms and effects of cervical spine rotation and extension on vertebral artery blood flow have been investigated and continue to be studied by a variety of methods including cadaveric studies (Toole and Tucker 1960), angiography (Licht et al. 1998), Doppler sonography (Haynes 1996) and magnetic resonance angiography (Wintraub and Khoury 1995). Despite these continuing efforts the exact aetiology of cervical artery dissection is unclear (Haneline and Rosner 2007). However, the relationship of the biomechanical forces imposed by manipulative therapy on the upper cervical segments and the coherence of the vertebral artery and/or the internal carotid artery with or without pre-existing vascular pathology encompass the most commonly accepted theories to explain this apparently complex and multifactorial event (Haneline and Rosner 1996, Kawchuk et al. 2008).

Injury to the vertebral artery system associated with cervical spine manipulative therapy may be explained in three ways. First, injury may be considered to be purely coincidental, the ascription of culpability based on a close temporal relationship. Secondly, injuries may be thought of as iatrogenic, the therapist causing trauma to a normal or susceptible arterial wall producing vasospasm and/or thrombosis and/or embolisation. Thirdly, some patients may be vulnerable to arterial dissection because of a congenital malformation such as hyperplasia or a pre-existing pathology such as osteophytic impingement (Cagnie 2005).

It has been suggested that smaller calibre vessels may have an increased risk of vascular pathology and therefore be more susceptible to disturbance by external mechanical stimuli (Haynes 1996). Perhaps more commonly biomechanical stress produces a tear of the intima and possibly the tunica media that leads to dissection of the arterial wall, the formation of a pseudoaneurysm with subsequent thrombus formation and stenosis (Di Fabio 1999). It is hypothesized that mechanical irritation of the endothelium may also cause the release of vasoconstrictors that produce vasospasm and thrombi (Fast et al. 1987). Other potential pathological mechanisms include the formation of intramural haematoma secondary to the rupture of the vasa vasorum, reflex vasospasm caused by mechanical irritation of the vessel or excitation of the sympathetic nerves (Frumkin and Balou 1990).

Emboli produced by the vertebral artery can travel to the distal basilar artery and its associated vessels. The signs and symptoms of ischaemic neurological insult will depend on the obstructed vessel and the neurological structures supplied by it. In cases where cervical spinal manipulation produces sub-clinical damage to the tunica intima or tunica media, progressive or delayed symptoms may occur as a result of the gradual proliferation of thrombi, emboli or progressive dissection (Palastanga and Boyling 1994, Boyling and Jull 2004). As a consequence neurological signs and symptoms may commonly be delayed and/or progressive.

A recent review of the empirical evidence supports the various biomechanical and pathophysiological models used to explain cervical artery dissection. This review emphasises the multidimensional and complex nature of the event and the variety of conceptual and methodological issues that have yet to be resolved (Kerry et al. 2008).

The vertebral arteries and the internal carotid arteries may be considered to be an integrated haemodynamic compensating system and it has been asserted that the emphasis of the impact of cervical spine manipulative therapy on the vertebral artery maybe misleading (Kerry et al. 2008). Dissection of the internal carotid artery, although less frequent than the vertebral artery, can occur (Lee et al. 1995). Initial findings from cadaveric studies (Toole and Tucker 1960) found that a decrease in contra-lateral vertebral artery blood flow on cervical spine rotation have been confounded by later *in vivo* studies (Licht et al.1998). These apparently contradictory results are thought to be a consequence of both the difficulty of obtaining accurate blood flow data as the vertebral artery crosses the atlas and a lack of methodological standardisation (Kerry et al. 2008). There are relatively few studies about intracranial blood flow (Kerry et al. 2008). The balance of evidence suggests that pre-manipulative screening protocols are not sufficiently sensitive or specific

to identify individuals who are at risk of injury from cervical spinal manipulation (Kerry et al. 2008). The precise relationship of vertebral artery blood flow to individual patient signs and symptoms is unclear (Kerry et al. 2008) and it is concluded that while there is an overall trend suggesting that both vertebral artery and internal carotid artery blood flows are influenced by full-range cervical movement, on the basis of current research it is apparent that no correlation between cervical spine rotation and vertebrobasilar symptoms can be clearly established (Kerry et al. 2008).

4. Aims and objectives

The aim and purpose of this research project was to:

i) Establish a definition of adverse events applicable to manual therapies and to categorise and classify data pertaining to adverse events in the literature.

ii) Provide a synthesis of data about adverse events within manual therapies to help inform the osteopathic profession about risk associated with common practices such as manipulation.

iii) To enable osteopaths to satisfy the obligation of obtaining informed consent as defined by statute.

To achieve the above our objectives were to conduct:

i) A modified Delphi consensus study using experts to create a definition of adverse events within the context of manual therapy.

ii) A systematic review of the literature to:

a) Provide a synthesis of the available data about the prevalence and incidence of adverse events associated with our predefined definitions of manual therapy.

b) Explain and provide evidence about the risks associated with different types of physical interventions.

c) Explain and provide information about the nature and type of adverse events that may occur with manual therapy.

5. Methodology

This project was divided into two distinct phases. The first phase involved conducting a Delphi consensus study. Full details of this study are contained within a paper that has been submitted for publication in a peer-reviewed journal (Appendix A). Therefore, this current report concentrates on the second phase of the project, namely a systematic review of the published literature.

A systematic review involves a rigorous review of all literature in a designated topic area. The tenets of a systematic review are that the search strategy for literature is comprehensive and inclusive, the selection of articles is clear and rationale, the data extraction is exact and the results and conclusions are reproducible should other researchers wish to validate or test your findings.

5.1 Scope of the study

To provide the boundaries and scope of the study, definitions were needed that could be applied when conducting the systematic review and they are used throughout this report.

Definitions

Adverse events

We used a modified Delphi consensus approach (we used a >75% agreement rule rather than 100% agreement rule) to establish a definition of adverse events for manual therapy. A Delphi consensus study is a questionnaire survey of expert opinion conducted in 'rounds'. Responses to each round of questionnaires are fed anonymously back to participants until an agreement or consensus is evolved or established. We selected this approach both to avoid key individuals' views dominating any open discussion and to ensure we could achieve international representation on our panel. Details of this study are in Appendix A. Initially, members of a focus group defined a hierarchical taxonomy for adverse events based on experience and taxonomies used in other professions. They also provided the content for the first round of the Delphi questionnaire. A panel of 50 experts then determined meaning and assigned a definition/description to each of the following four categories of adverse events: 'major'; 'moderate'; 'minor'; or 'not adverse' events.

We subsequently used these criteria, when conducting the systematic review, to classify signs and symptoms as presented in the literature and graded them accordingly as adverse events.

Manual therapists

We defined manual therapists as statutory regulated or registered professionals who administer manual therapy. Manual therapists, including chiropractors, osteopaths and physiotherapists administer non invasive therapeutic interventions that involve physical contact and which may or may not involve the use of mechanical and or electrical devices.

We appreciate that statutory regulation varies between countries and that there are non-statutory regulated manual therapists administering other forms of manual therapeutic interventions such as Bowen technique, Rolfing, vibration therapy and massage. These do not have statutory recognition and, or rarely, have a single registration body. Consequently, standards of training and practice may not be subject to the same degree of regulation, rigour and scrutiny as statutory regulated professions. We therefore decided to include only those studies where the therapist and/or therapy were clearly defined and stated, fitted our description of manual therapists and were recognised by a statutory regulated professional body.

Manual therapy

The study team defined manual therapy as practitioner administered manual interventions that involve physical contact and do not include any mechanical devices. Where appropriate, we have categorised therapies using criteria proposed by Gross et al. (2002). They identified three types of intervention: manual therapy including but not limited to manipulation (high velocity, small or large amplitude techniques); mobilisation (low grade velocity, small or large amplitude techniques, neuromuscular techniques and cranio-sacral); and massage (other soft tissue techniques).

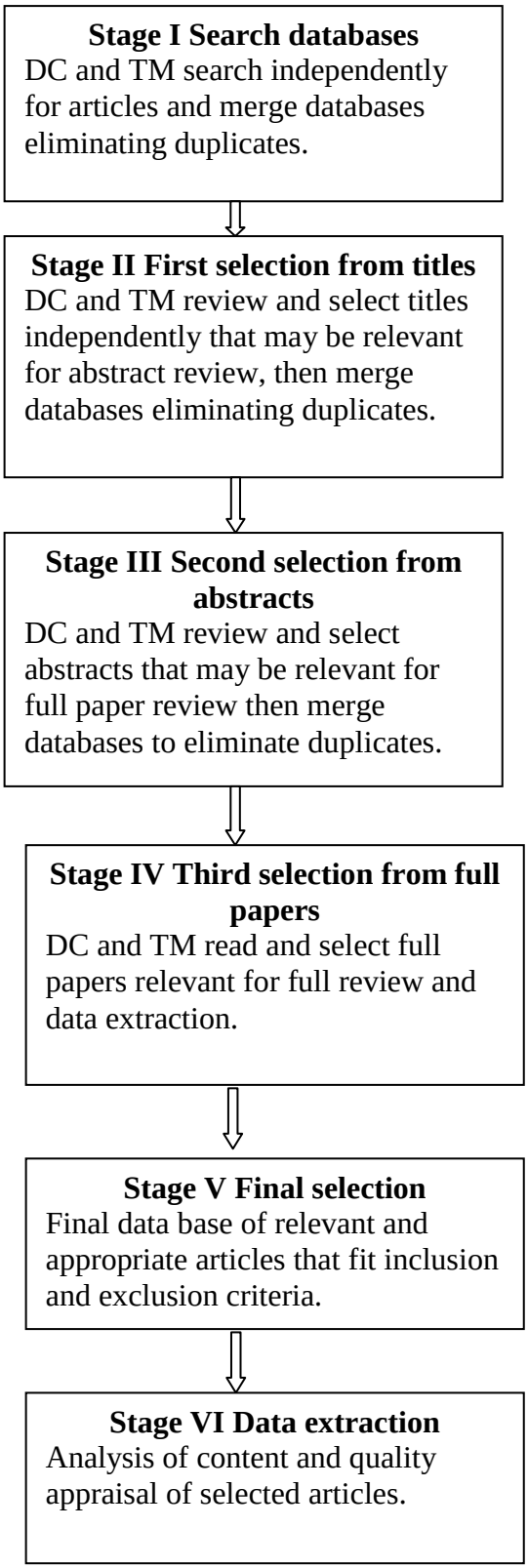
Typical manual treatments, however, are often multi-modal interventions. Practitioners, depending on their analysis of the patient presentation, case history, medical history and contra-indications, will deploy a variety of techniques aimed to produce a therapeutic benefit. Techniques focus on improving joint health and function and may include passive articulation, springing, traction, harmonic oscillations and high or low velocity, high or low amplitude, short and/or long lever thrusts. Each of these approaches may be used in combination, with or without exercise prescription, and may be utilised with other therapeutic modalities such as acupuncture or various forms of electrotherapy, mechanically assisted manual therapies using equipment such as traction tables or employ mechanical devices such as the “activator instrument” used in chiropractic adjustments. In many cases manual therapy is administered concurrently with medication. All such approaches are deemed non-manual and are excluded from this review. However, we did include

some pragmatic studies where multi-modal/mixed interventions were administered, but only if it was clearly stated that the non-manual element was minimal (less than 90-95% of the overall intervention). Our search terms, and inclusion and exclusion criteria used for selecting articles for the systematic review reflect this variety.

5.2 Systematic literature review: protocol and procedures

Two researchers (DC and TM) searched, reviewed and selected articles independently (Figure 1). At each stage of selection, chosen articles were compared. At the title and abstract selection stages, any articles that were not jointly agreed for selection went through to the next stage. At final selection for full paper review, if there was found to be any disagreement about inclusion a third party independent reviewer would be commissioned (MU) to arbitrate and make the final decision. This was, however, found to be unnecessary as there were few borderline issues within the final set of articles.

Figure 1 Review stages



5.3 Searches

Terms used in the literature search were derived from prior familiarisation with the literature and brainstorming within the study team. The key search terms used at stage I are shown in table 1. Search engines' functions, layouts and programmes differ so we prioritised search terms into 'high' and 'medium to low' use. Search strings were developed and modified as required for each of the different databases and are illustrated in table 2. All high priority terms were included in our searches and where possible we included some or all of the medium to low priority terms.

Table 1 Key Search Terms

High priority terms (must be included in the search strings for each database)	**Medium/low priority** (may be included in search strings should the database search engine allow more characters)
Osteopathy, Osteopath, Osteopathic (Truncation osteop*) Chiropractic, chiropractor (chiropract*) Physiotherapy, physiotherapeutic, physiotherapist (physio*) Manual therapy/therapies/therapist, (manual or therap*) Orthopedic, orthopaedic	Medical and general practitioner Manipulative therapist Bone Setter Massage therapist
Manual Therapy see above Manipulation, Manipulatory, Manipulations manipulat* Cavitation, Cavitations cavitation* Adjustment Articulation, Mobilisation	Soft tissue, Muscle energy, Stretching, Massage, Thrust (High/low velocity, minimal, leverage), Kneading, Effleurage, Inhibition, Springing, Traction, Vibration Treatment, treatments treatment* Technique Techniques technique*
Adverse event, Adverse events (adverse and event* or effect* etc) Adverse effect, Adverse effects Adverse reaction, outcome, complication, response Side effect, Side effects (side effect*)	Injury, Accident, Trauma, Incident, Serious, Major, Significant, Minor, Moderate, Mild, Medium, Severe, Expected, Unexpected, Permanent, Transient, Unforeseen, Unintentional, Chance, Unexpected, Unplanned, Hurt harm, Damage, Insult
Spine, spinal Muscle Disc Body	Cervical, Thoracic, Lumbar, Joint, Dissection, Insufficiency, Fracture, bone, spasm, insufficiency, tear, dislocation, fracture, subluxation, infarct, cauda equina, loss, pain, stroke, TIA Vertebra*

Table 2 Examples of search strings

1.(Osteopath* or chiropract* or physio* or manual and therap*) and (side effect or adverse and reaction or effect or event or outcome or response or complication or injury or accident) and (manipul* or mobilis* or cavitation* or adjustment or massage or soft tissue or technique or stretching or spine or muscle or disc or joint or body)

2. (Osteopath* or chiropract* or physio* or manual and therap* or practitioner or orthop*) and (serious or major or severe or mild or transient or constant or moderate or medium or significant or unexpected or unacceptable or complication) and (side effect or adverse and reaction or effect or event or outcome or response or complication or injury or accident or harm) and (manipul* or mobilis* or cavitation* or adjustment or articulation or massage or soft tissue or technique or stretching or spine or muscle or disc or joint or body)

We searched the following major scientific databases (Medline, OVID, Science Direct, Web of Science) and smaller profession-specific databases (PEDro (physiotherapy database), Index of chiropractic and AHMED (Allied Health Medicine)) plus other peripheral databases that we thought may increase the breadth and width of our search, these are shown in table 4 (in Section 6: Results). Databases were searched from inception to the current date of the search (March 2008). We also used citation tracking from our selected full articles to ensure that our searches were inclusive.

5.4 Selection of articles (Stages II -V)

Due to the diverse nature of the subject area we developed detailed inclusion and exclusion criteria. As there are many forms of manual therapy, types of treatment and therapists, the inclusion and exclusion criteria aimed to create a more homogenous database of studies.

Selection criteria

Inclusion criteria
Statutory registered professional(s) or regulated professional(s) in a manual therapy.
Intervention or therapy must involve physical and/or manual contact to an individual with therapeutic intent, administered without the use of mechanical, automated, electronic, computer or pharmacological aides/products.
Adults and children.
Patients must be conscious during the intervention.
RCTs, cohort studies, observational studies, systematic reviews, case control studies, case series.
Peer reviewed literature only.
New/original data about adverse events with manual therapies.

Exclusion criteria
Non-peer reviewed literature: this included reviews, letters and editorials.
Case studies.
Mixed interventions, multidisciplinary where response to manual therapy elements would be unclear/undeterminable.
Non-manual therapies including: the use of equipment, pharmaceutical, psychological, faith healing interventions.
Self-administered therapy, including exercise programmes.
Manual techniques applied to non- conscious patients (anaesthetised and cadavers).
RCTs prior to 1997.

5.5 Quality appraisal

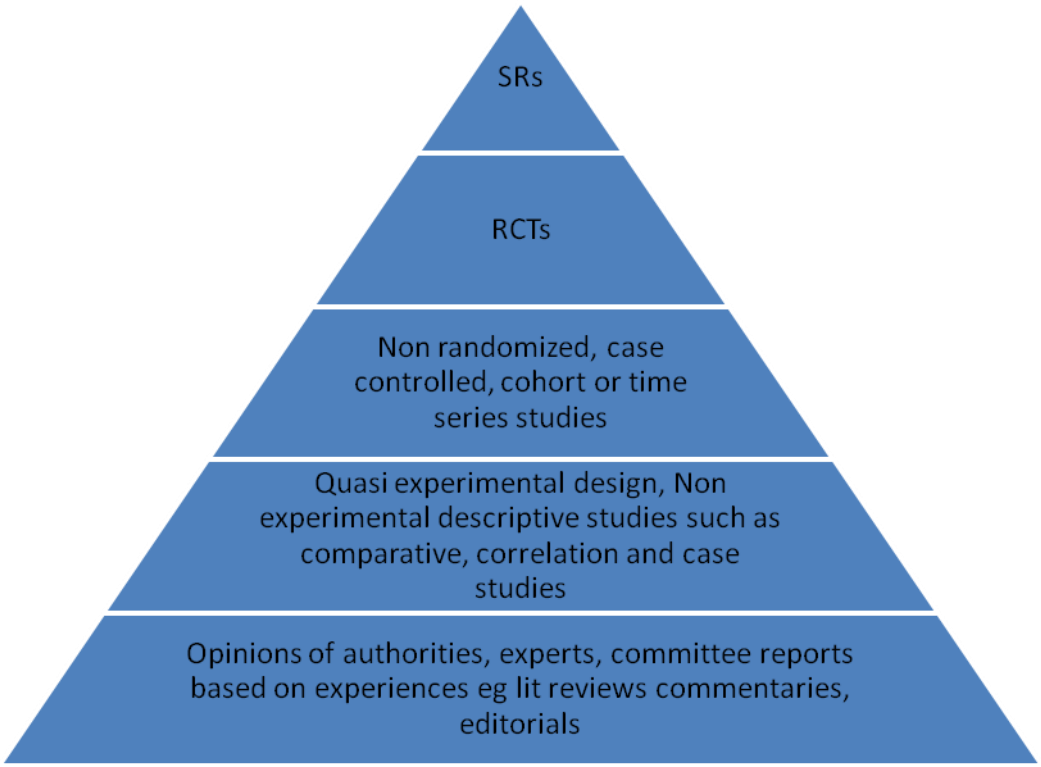
Generic quality appraisal criteria were used to assess the overall quality of the articles, other than RCTs, reviewed at stage 6 (full paper review data extraction) (Critical Appraisal Skills Programme CASP 1999 www.phru.nhs.uk/CASP/critical_appraisal_tools.htm : accessed May 2008).

Additionally, we used specific criteria to assess the quality of adverse event data we extracted for analysis. The quality appraisal criteria and the detailed assessment of each study are shown in Appendix C. In addition, the quality criteria rating outcome was used to assess the quality of adverse event data collection methods. We graded the assessments from highest to lowest: High – majority of appropriate quality criteria were satisfied (80% plus); Medium – most of the appropriate quality criteria were satisfied (60 -79%); Low – below 60% of the appropriate quality criteria were not satisfied. Narrative comments were recorded where there were quality issues with study methodology.

The RCTs were assessed for quality based on Koes's (1995) criteria for quality appraising musculoskeletal RCTs. This method gave a score out of 100, 100 indicates maximum quality. Seventeen quality criteria were used and weighted according to importance. Scores below 60 indicate serious quality issues.

Each article was categorised according to the methodological approach used to conduct the research it was graded as I to V depending on its place the hierarchy of levels of evidence (adapted from Grimshaw and Eccles from Silagy and Haines 1998) shown in Figure 2. Each article was given a quality score.

Figure 2 Hierarchy of evidence (Highest level I at top of pyramid)



The hierarchy of evidence ranges from Level I, systematic reviews (SRs) with meta-analyses to level V evidence based on authority, clinical experience i.e. descriptive studies, case histories and reviews. Level V literature was not included in this review as the evidence was deemed too weak, the exception were literature reviews that presented some synthesis of data or original data. The best evidence research for our purposes are systematic reviews with meta-analyses of prospective cohort studies with a comparative control group (Level I), followed by RTCs reporting adverse events and prospective cohort studies and observational studies. As this review is about risk we will classify prospective cohort studies as level II evidence.

All articles are ranked in the tables by level of evidence first followed by quality assessment ranking.

5.6 Data analysis

The purpose of the analysis was to address the objectives of the study, namely to provide a synthesis of information on prevalence and incidence of adverse events associated with manual therapy, as well as evidence on risks and information about the nature and type of adverse events. Initially we calculated the relative risk (RRs), where appropriate, this data indicates the risk of an event relative to exposure. It is the ratio of the probability of adverse events occurring in a manual therapy group to another group (Bland and Altman 2000).
For example:

	Number of adverse events occurring	Total in group
Manual therapy	A	B
Other therapy	C	D

So the RR is calculated by dividing (A/B) / (C/D). We set the confidence interval (CI) at 95% to indicate the level of significance of the RRs. Where the CI spans either side of one the data is unlikely to significant i.e. we can be 95% certain that the statistic is a chance finding and the probability of having an adverse event could be equal regardless of treatment group.

Where appropriate we performed a meta-analysis on the data collected. These data are presented in the form of Forest plot, which graphically shows the RRs and CIs. The study data are weighted according to the number of participants so the statistical power of results can be gauged. Where this

was not possible we present data from individual studies qualitatively.

We aimed to extract incidence, risk and nature and type data. We synthesized these data from the most homogenous studies e.g. prospective cohort studies, surveys, RCTs and systematic reviews.

Incidence

Incidence in this study is defined as the rate or frequency with which adverse events occur over a period of time (incidence reflects the occurrence/frequency of new cases of the condition of interest, over a defined period of time, estimated by counting the number of new cases of the condition in a population for a defined period and dividing this with the total amount of the population at risk (Greenberg et al. 2001)). The quality of incidence data is determined by the accuracy of the estimates used as numerators and denominators.

We organized the data into:

i) Patient incidence data from cohort and observational studies and surveys
   Therapists reporting adverse events in their patients and reports from patients who had received manual therapy.
ii) RCT incidence data.
iii) Population incidence data from population studies.

These data show estimates of incidence in the general population based on epidemiological data.

We considered reporting prevalence, defined as the amount of adverse events that present at a specific time point post manipulation or manual therapy (Greenberg et al. 2001) but prevalence data is of less value than incidence data as they do not reflect the number of adverse events that occur either before or after the time point in question.

Risk

To assess risk we extracted any data comparing the occurrence of an adverse event with any other variable or factor. These data can be presented as percentages, correlations, associations and ratios. We collated this data and recorded the overall association whether it was positive, negative and or no difference, we then extracted data about significance of the findings and where possible if this information was not available we calculated these ourselves.

Nature and Type of adverse events

The variety of adverse events and the reporting rates were recorded. We extracted data about onset of adverse events and their duration.

6. Results

- **Section 6.1** presents a brief summary of the Delphi study the full of which are shown in Appendix A.
- **Section 6.2** gives the results of the search for literature and the selection process.

The sections following 6.2 present analyses of data extracted from the articles reviewed. We also report on the quality of studies included in the review.

- **Section 6.3** shows incidence data for adverse events at an individual level, in RCTs and at a population level.
    a. At the individual level we report data from patients, manual therapists and non manual therapists, we include data from prospective cohort studies specifically designed to explore the incidence of adverse events in patients.
    b. We also show data from RCTs that reported incidence of adverse events as an outcome measure. We present relative risk data for experiencing adverse events in a controlled and assessed environment with carefully screened participants within manual therapy and non manual therapy treatment groups.
    c. Finally we report population data looking at incidence data in larger communities.
- **Section 6.4** shows data about risk factors that may be associated with patients having or reporting adverse events.
- **Section 6.5** describes the nature and type of adverse events we assess:
    a. the onset of adverse events
    b. the duration of adverse events,
    c. the residual effects of adverse events and their effect on daily living and
    d. reported fatalities.
- **Section 6.6** gives a narrative overview of findings from both systematic and literature reviews publishing and analysing research in the field of adverse events

6.1 Delphi Study results

A layered, pragmatic definition for adverse events was agreed through the Delphi consensus study, and is summarised in Table 3 (for full details see Appendix A). These terms are applied throughout this report.

Table 3 Key summary table of definition of adverse events in manual therapy

Adverse Event	Duration*	Severity	Description
Major	Medium/long term	Moderate/severe	Unacceptable Requires further treatment Serious Distressing
Moderate	Medium/long term	Moderate	
Minor	Short term	Mild	**Non-**serious Function remains intact Transient/reversible No treatment alterations required Short term consequences Contained
Not adverse	Short term	Mild	

*long term = weeks, medium term = days, short term = hours

6.2 Systematic review: search and selection results

The initial searches at stage I when merged produced a study database of 19,953 articles. Table 4 shows the results from each database search contributing to this total. There were many duplicates due to the overlap in database content from Medline.

Table 4 Databases searched (March 2008)

	Hits TM	Hits DC
Main databases		
PubMed	4059	7401
OVID (inc chiroaccess)	2812	7056
Science Direct	1187	824
ISI Web of Science	249	242
Wiley Interscience	119	824
Index of Chiropractic Literature	968	259
PEDro	213	330
Other databases		
Taylor and Francis Informaworld	685	
Cambridge Journals		445
Ostmed	Non-operational	
AMED		233
JAMA		851
Total excluding duplicates	9,960	15,991
Total combined excluding duplicates	19,953	

The process of article selection and rejection from this point on is shown in Figure 3.

Stage I, II and III

The 19,953 titles were reviewed and 1,564 titles were selected for abstract review. Of these abstracts we selected 390 abstracts for full paper review, these were divided into two databases. One hundred and sixty abstracts were selected as directly relevant adverse event studies and 230 abstracts were classified and selected as potentially relevant, i.e. RCT and cohort studies that were testing manual treatments that may report adverse events.

We sorted the remaining unselected abstracts, from stage 3 into four different databases, and reviewed them as necessary to inform our introduction and discussion. They were not used to provide evidence about adverse events.

i) 174 abstracts were studies that were about patho-physiological processes that occur with manual therapies, these were mostly experimental studies and were reviewed to inform the introductory section about patho-physiology.

ii) 284 abstracts were about case studies, these were not reviewed because they are generally not peer reviewed or did not constitute original research, i.e. descriptive only and level V evidence.

iii) 214 abstracts were summaries of editorials, reviews and commentaries, therefore level V evidence and so rejected for review.

iv) 502 abstracts were rejected because:

Adverse events were not used as an outcome measure or reported
They were efficacy studies with mixed interventions
Pharmacological intervention studies
Cadaver studies
Participants were anaesthetised (i.e. manipulation under general anaesthetic)
Surgical procedures
Not relevant, different topic area

From citation tracking we identified 13 papers and accepted 3 for full paper review.

Stage IV and V

Three hundred and ninety articles were reviewed and grouped into two final databases. One database included articles reporting adverse events as the primary outcome (main adverse event data base) and the second, included those reporting adverse events as a secondary outcome of interest.

Of the 160 main adverse event articles reviewed at stage IV, we rejected 103 for reasons shown in Figure 3. This left 60 articles for full review and data extraction and from these we were able to extract data about adverse event incidence, risk factors associated with adverse events and the nature and type of adverse events (table 5). Of these were four articles where authors reported on the same dataset in two separate articles (Haldeman (2002a and 2002b), Hurwitz (2004 and 2005) Rubinstein (2007 and 2008) and Senstad (1996 and 1997)). Each dataset was treated as one article to avoid double counting.

There were 230 RCT and cohort study articles selected for review. Due to the large number of articles and the general poor reporting of adverse events (Bronfort 2001 and Ernst1999), we decided to review only RCTs that were published after the CONSORT guidelines for reporting RCTs was published in 1996. These guidelines advised authors to record and report adverse events as part of their protocols. In the revised CONSORT statement (Altman et al. 2001 and Moher et al. 2001) and in the extension of the CONSORT guidelines in 2004 (Ioannadis et al. 2004) further advice was given to include more detail about the reporting of harms. Additionally in the European Guidelines (2004) for RCTs, there is a requirement to report any serious adverse events to the trial registering body and the steering group and data monitoring committees. We rejected 42 articles because they were published before the CONSORT statement in 1996. Figure 3 shows the reasons for rejecting articles at stage IV. Thirty six articles were selected for data extraction. On review, 5 articles reported duplicate data from a previously reported RCT, these were grouped and treated as one article (Hoving et al 2002 and 2006, Hurwitz et al 2002, 2004 and 2005, Hurwitz et al 2002 and 2006 and Skargren et al 1997 and 1998). One article reported adverse event data but it was unclear which treatment arm it related to (Schiller 2001) this was excluded leaving a total of 30 articles for data analyses.

Figure 3 Progress of review

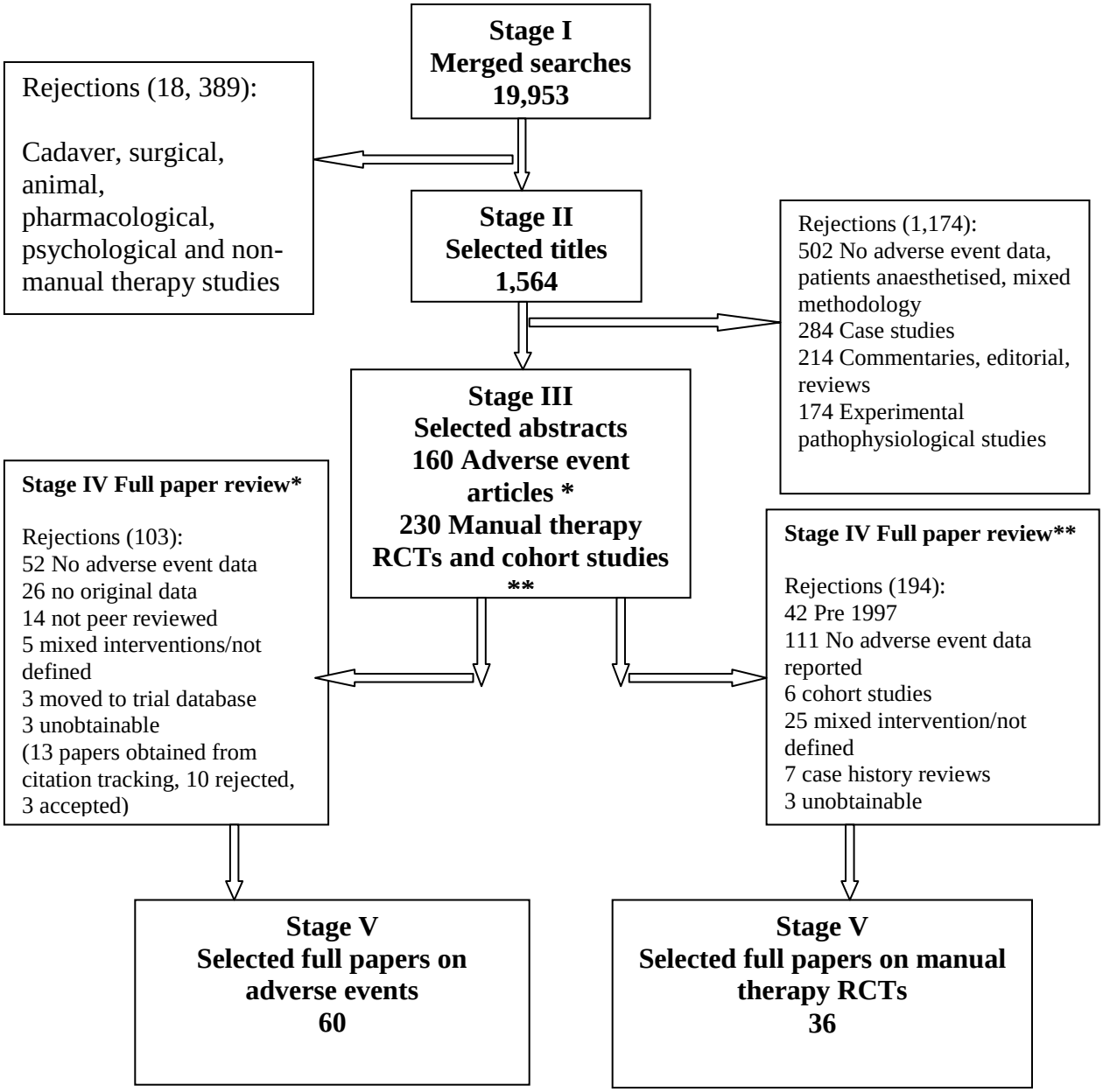


Table 5 Articles containing information on adverse events

Study incidence (20)	Population incidence (23)	Risk factors (28)	Nature and Type (36)	RCTs (30)
Adams (1998)	AndersonPeacock (2005)	Assendelft (1996)	Abbot (1998)	Bove (1998)
Barrett (2000)	Boyle (2008)	Barrett (2000)	Adams (1998)	Brontfort (2001)
Bronfort (2001)	Carey (1993)	Cagnie (2004)	Barrett (2000)	Burton (2000)
Cagnie (2004)	Cashley (2007)	Cassidy (2008)	Cagnie (2004)	Cherkin (2001)
Egizii (2005)	Coulter (1998)	Dittrich (2007	Carey (1993)	Cleland (2007)
Ernst (2001)	Dabbs (1995)	Dupeyron (2003)	diFabio (1999)	Evans (2003)
Garner (2007)	Dupeyron (2003)	Dziewas (2003)	Dupeyron (2003)	Ferreira (2007)
Hurwitz (2004)	Dvorak (1985)	Gross (2007)	Dvorak (1985)	Giles (1999)
Hurwitz (2005)	Dvorak (1993)	Haldeman (1999)	Dvorak (1993)	Giles (2003)
Leboeuf Yde (1997)	Hurwitz (1996)	Haldeman (2002)	Dziewas (2003)	Haas (2004)
Lee (1995)	Haldeman(2002)	Haneline (2003)	Egizii (2005)	Hancock (2007)
Malone (2003)	Haneline (2003)	Haneline (2005)	Ernst (2007)	Hawk (2005)
Margarey (2004)	Klougart (1996)a	Hufnagel (1999)	Haldeman (1999)	Hawk (2006)
Michaeli (1993)	Klougart (1996)b	Hurwitz (2004)	Haldeman (2002)	Hay (2005)
Rivett (1997)	Lee (1995)	Klougart (1996)b	Haldeman (2002)	Hoeksma (2004)
Rubinstein(2008)	Malone (2003)	Leboeuf Yde(1997)	Haldeman (2002)	Hondras (1999)
Senstad (1996)a	Margarey(2004)	Masalchi (1997)	Hufnagel (1999)	Hoving (2002)
Senstad (1996)b	Michaeli (1993)	Michaeli (1993)	Hurwitz (1996)	Hsieh (2002)
Senstad (1997)	Oliphant (2004)	Oppenheim(2005)	Hurwitz (2004)	Hurwitz (2002,4,5)
Thiel (2007)	Rivett (1996)	Reuter (2006)	Hurwitz (2005)	Hurwitz (2002,6)
	Rothwell (2001)	Rothwell (2001)	Klougart (1996)a	Jull (2002)
	Senstad (1996b)	Rubinstein (2008)	Klougart (1996)b	Nelson (1998)
	Thiel (2007)	Rubinstein (2005)	Leboeuf Yde(1997)	Plaugher (2002)
		Senstad (1996a)	Lee (1995)	Santilli (2001)
		Senstad (1996b)	Malone (2003)	Sawyer (1999)
		Smith (2003)	Margarey (2004)	Skargren (1997,8)
		Terrett (1997)	Michaeli (1993)	Strunk (2008)
		Thiel (2008)	Oppenheim (2005)	Tuchin (2000)
			Reuter (2006)	UK BEAM (2004)
			Rubinstein (2007)	Vincenzino (2001)
			Senstad (1996)a	Williams (2003)
			Senstad (1996)b	
			Senstad (1997)	
			Terrett (1997)	
			Thiel (2008)	
			Vohra (2007)	

Quality of studies

The main adverse event studies ranged in quality and type, and consisted of retrospective surveys of case studies, case notes, questionnaire surveys, observational studies and prospective cohort studies. The quality of adverse event data collection and reporting ranged from high to low (Appendix C). 43 % (26) were rated as high quality, 37% (22) were rated as medium quality and 20% (12) as low quality. The RCT quality scores ranged from 32 to 84, the upper quartile range was 71 - 84, the upper inter quartile range was 58 – 70, the lower inter quartile range was 45 -57 and the lower quartile range was 32 – 44. Six of the 30 RCTs (20%) were scored in the upper quartile range, 5 (17%) in the lower quartile range, the remainder were in between.

Characteristics of studies

In the main adverse events database 33/60 of the research articles we reviewed were conducted by and/or funded by chiropractors. Thirteen studies were done by neurologists and medics, eight studies by physiotherapy/physical therapy or a physical medicine perspective, six had an academic research foundation and none were solely osteopathic (Appendix G). One prospective cohort study (Cagnie 2004) and two RCTs included Osteopaths (Williams 2003 and UK BEAM 2004) included Osteopaths. From the main trial data base 18 studies were done in Europe, six in the UK, 15 in the USA or Canada and four in Australia or New Zealand, the remaining studies were database searches. From the original 36 trial papers, nine were from Europe, six from the UK, 16 were from the USA or Canada, four from Australia and one from South Africa. The majority of the studies investigated spinal manipulation.

6.3 Data Extraction - Incidence data

Individual data from cohort and observational studies and surveys

Incidence reports of adverse events varied according to whether they were reported by the therapist administering the treatment, derived from patient self reports or from therapists seeing a patient who had not administered the treatment. The severity and nature of the adverse event (muscle soreness to vertebral artery dissection (VAD)) and the data collection method also produced variability. We categorized the data into homogenous groups for ease of analysis and to indicate quality of evidence. The Roman numerals indicate level of evidence and hi (high), med (medium), lo (low) indicate quality of the study.

Table 6 shows the data extracted from 4 articles reporting data from manual therapists about their patients. Table 7 shows data about adverse event cases reported by non-manual therapists and Table 8 shows data reported by patients about adverse events after treatment. Detailed content analysis of these articles can be found in appendix B.

Therapist reports of adverse events with manual therapy

Seven articles contained data about therapist/clinician reports of adverse events amongst their patients, four articles contained data from manual therapists and three had data reported by neurologists about patients seeking care from them as a result of manual therapy.

Table 6 Therapists' report of adverse event incidences in patients they have treated

Author, (evidence level and quality)	**Therapists/Clinicians**	**Adverse event experience/report**
Reports by manual therapy trained therapists/clinicians		
Egizii (2005) Qu'aire survey IV Hi	GPs and other specialists trained in osteopathy	26.4% (37/140) osteopathic trained medics reported adverse events (unspecified) occurring as a result of a treatment (manipulation) they had administered during their careers
Adams (1998) Qu'aire survey IV Med	Manipulative orthopaedic specialists and manipulative physiotherapists	19% (25/129) of the physiotherapists reported adverse events occurring as a result of a manipulation they administered during their careers
Margarey (2004) Qu'aire survey IV Med	Manipulative physiotherapists	98.7% (447/453) reported experience of patients having an adverse event occurring as a result of treatment or examination of the cervical spine over the whole of their careers (from a list of 291 signs and symptoms)
Michaeli (1993) Qu'aire survey IV Med	Physiotherapy reports of adverse events post treatment responded about their practice.	Reported 153 complications after cervical spine manipulation and mobilisation but incidence figure cannot be determined as no denominator data included
Reports by medically trained non-manual therapy clinicians (i.e. manipulation not administered by themselves)		
Rivett and Milburn (1997) Qu'aire survey IV Hi	Neurologists, orthopaedic specialists, vascular surgeons: case files over a 5 year period	15.8% (23/146) reported seeing patients who had complications post manipulation over 5 years
Lee (1995) Qu'aire survey IV Med	Neurologists reporting patients with neurological complications occurring after manipulation over a 2 year period	29% (51/177) of neurologists responding to a survey, reported seeing patients with strokes, myelopathies or radiculopathies occurring post manipulation (within 24 hours) over a 2 year period
Malone (2002) Retrospective case review IV Lo	Neurologist cases of patients post manipulation with adverse events, over 5 years in a neurology clinic with: worsening symptoms; irreversible symptoms	18.6% (32/172) saw patients who were worse after manipulation 12.2% (21/172) saw patients with irreversible symptoms after manipulation

Manipulative therapist reports of patients experiencing at least moderate adverse events as a result of treatment they administered, ranged from 19% to 98.7%. The large range in the results is due to the data collection methods (e.g. pre-defined tick list or recall) and the type of adverse events the therapists were asked to report (e.g. major or minor).

Between 15.8% and 29% of non-manual therapists (neurologists) surveyed reported seeing patients admitted to their care who had had complications after manipulative treatment. Combining the data from all three surveys gave a sample of 495 secondary care physicians: of these 106 (21%) recalled treating patients with complications, or who were worse, after manipulation/manual therapy. The majority of responses were from USA physicians (349), the remainder were from New Zealand (146).

Patient reports of adverse events

There were eight prospective cohort studies specifically designed to investigate adverse events with manual therapy. These studies represent at least 42,451 manual therapy treatments that included manipulation in 22, 833 patients. There were two studies reporting major adverse events. Senstad et al reported 14 cases of 'unbearably severe' side effects in 12 patients after treatment (12 of 1058 patients (1%)) and Thiel et al. (2007) reported a risk rate for serious adverse events 1-2: 10,000 consultations (approx 3 in 28,109 consultations (0.01%)). Between 34% and 60.9% (median 53%, mean ~46%) of patients reported at least one minor or moderate adverse event after a treatment (using criteria derived from our Delphi study). No significant, serious or major adverse events were reported.

Table 7 Patient report of incidence of adverse events after manual therapy treatment in prospective cohort studies[$] and adverse event RCTs*

Author(quality)	Treatment and patients	Adverse event experience/report
Barret and Breen (2000)[$] (Hi)	Patient self reported adverse events after first chiropractic spinal manipulation	53% (36/68) reported adverse events over 2 days 0% serious adverse events
Cagnie (2004)[$] (Hi)	Patient reported adverse events after chiropractic, osteopathic or physiotherapy spinal manipulative treatment	61% (283/465) reported at least one adverse event after treatment within 48 hours 0 serious adverse events reported
Hurwitz (2004 and 2005)* (Hi)	Patient reports of adverse events after chiropractic treatment for neck pain	30.4% (85/280) reported adverse symptoms at 2 weeks 0% reported major adverse events
Rubinstein (2008)[$] (Hi)	Patient reports of at least one adverse event after three treatments (chiropractic manipulative technique)	56% (296/529) after any of the first three treatments (13% were high intensity) 46% after the first visit (14% were high intensity) 22% after the second or third visit (15% were high intensity) 1% (5) reported being worse at 12 months
Senstad (1996a and 1997)[$] (Hi)	Patient reports of 'unbearably severe adverse reaction' after chiropractic spinal manipulative care	0.1% (12/1058) patients had 'unbearably severe side effects' occurring after treatment 55% of patients reported at least one AE during the course of treatment
Senstad (1996b)[$] (Hi)	Patient report of adverse events after chiropractic spinal manipulation	34% (125/368)patients experienced 'some sort of discomfort' after spinal manipulation 0 'serious incidents' after manipulation
Thiel (2007)[$] (Hi)	Patient / chiropractor report of significant adverse event after chiropractic cervical manipulation up to 7 days	0% significant adverse events after chiropractic manipulation Approx 0.01% (3) serious adverse events occurred immediately after treatment 1.3 to 1.6 (448) moderate adverse events occurred after cervical spine treatment Approx 4% (1124) headaches occurred after cervical spine treatments
Garner (2007)[$](Med)	Patient reports about chiropractic treatment over 17 months	0% (0/259) adverse events were reported or observed
Leboeuf-Yde (1997)[$] (Med)	Patient reports of at least one unpleasant reaction after chiropractic spinal manipulation	44% (275/625) reported at least one unpleasant reaction 0% reported major adverse reactions

Incidence of adverse events in RCTs

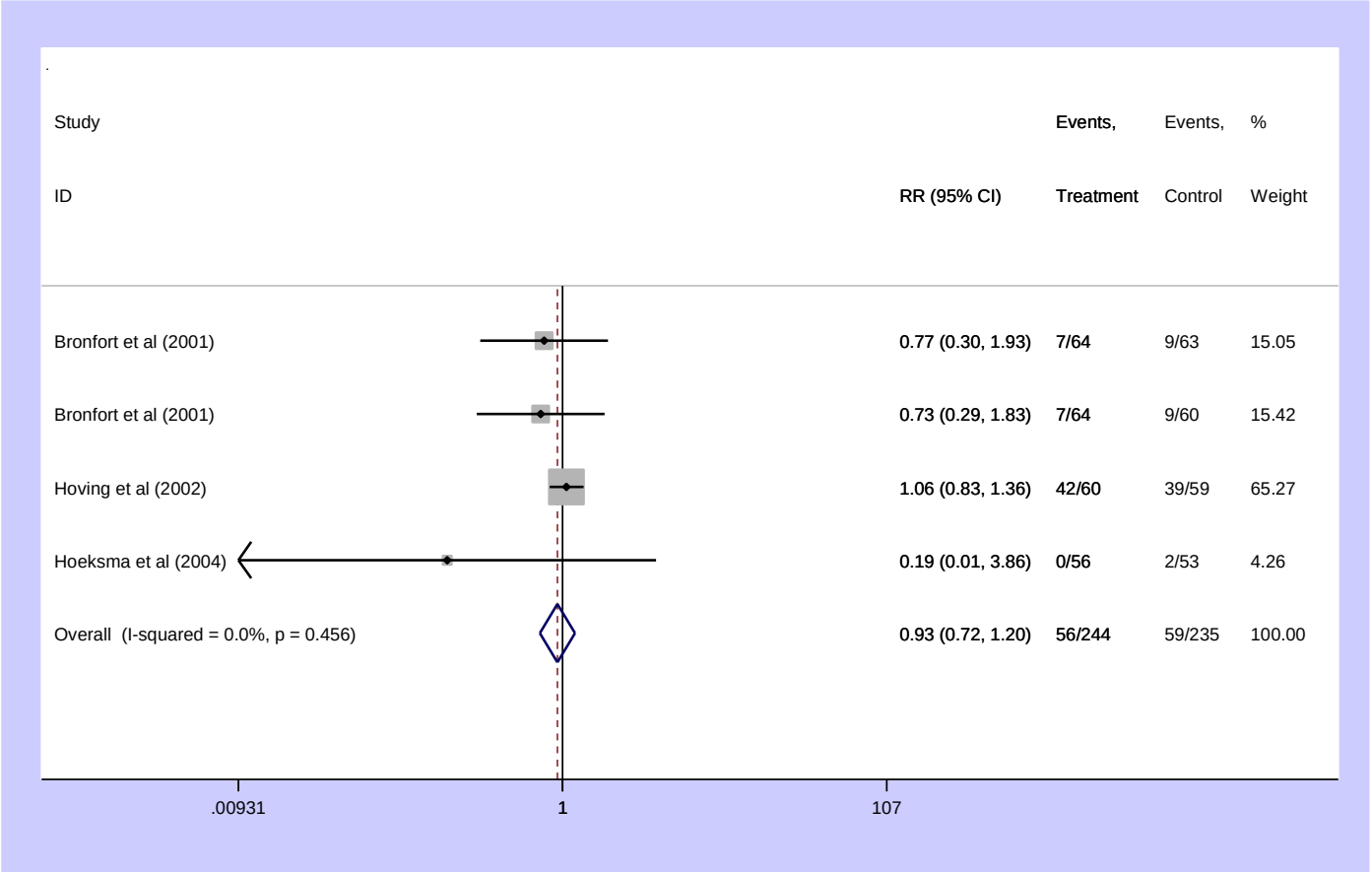
We identified 36 articles reporting 30 studies. Sixteen studies (N=1,543) did not report any adverse events occurring as a result of manual therapy (see Appendix E). No major adverse events, deaths or vascular insults were reported to have occurred in any of the studies reviewed.

We pooled data from the remaining 14 RCTs (N=5,550) that reported the occurrence of adverse events. Mild or moderate adverse events were recorded in 5.5% (155/2,797) of the manual therapy treatment participants and 6.4% (175/2,735) with controls, sham and other interventions.

Where possible we worked out the relative risk (RRs) of having an adverse event in the manual therapy arms of the trials compared with other treatment arms of RCTs. Figures 4, 5, and 6 show the risk of having an adverse event in the manual therapy arm of the trials with: exercise (Figure 4); medical care, drug or GP care (Figure 5); and other CAM therapies (Figure 6).

The quality of the trials in Figure 4 were high quality, the meta-analysis of data from these trials forest plot shows no statistically significant risk of having and adverse event with manual therapy or exercise. The manual therapies used in the Brontfort et al (2001) and Hoeksma et al (2004) RCTs included spinal manipulation. Hoving et al (2002) used passive articulation.

Figure 4 Relative Risk for adverse events with manual therapy vs exercise



The RCTs shown in Figure 5 were quite diverse as indicated by the high I square value. Nelson et al (1998) compared spinal manipulation with amitryptiline, Giles et al (1999) spinal manipulation and NSAIDs, Hoving et al (2002) manual therapy (passive mobilization) and GP care, Evans et al (2003) chiropractic care with medical care and Hancock et al (2007) spinal manipulation and diclofenac (NSAID). The studies varied in quality Giles et al (1999), Hancock et al (2007) and Evans et al (2003) scored 63, 56 and 53 out of 100 respectively, whilst Nelson et al (1998) and Hoving et al (2002) scored 75 and 84 /100 respectively (See appendix E). The forest plot (figure 5) shows the three RCTs comparing manual therapy specifically with drugs (Nelson et al 1998), Giles et al (1999) and Hancock et al (2007) favours manual therapy. We conducted a sensitivity analyses and found that the relative risk in these three drugs trials was 0.05 (95% CI 0.01 – 0.20) indicating that the risk of adverse events was greater in the drug arms than the manual therapy arms. The forest plot shows Evans et al (2003) and Hoving et al (2002) favour medical/GP care, we make the assumption that drug care was part of the standard care, but this was not clearly indicated. Combining all the trials comparing medical and drug care with manual therapy the overall the meta-analysis shows almost equal risk of having an adverse event in either arm of the trials.

Figure 5 RR for adverse events with manual therapy vs medical, drug or GP care

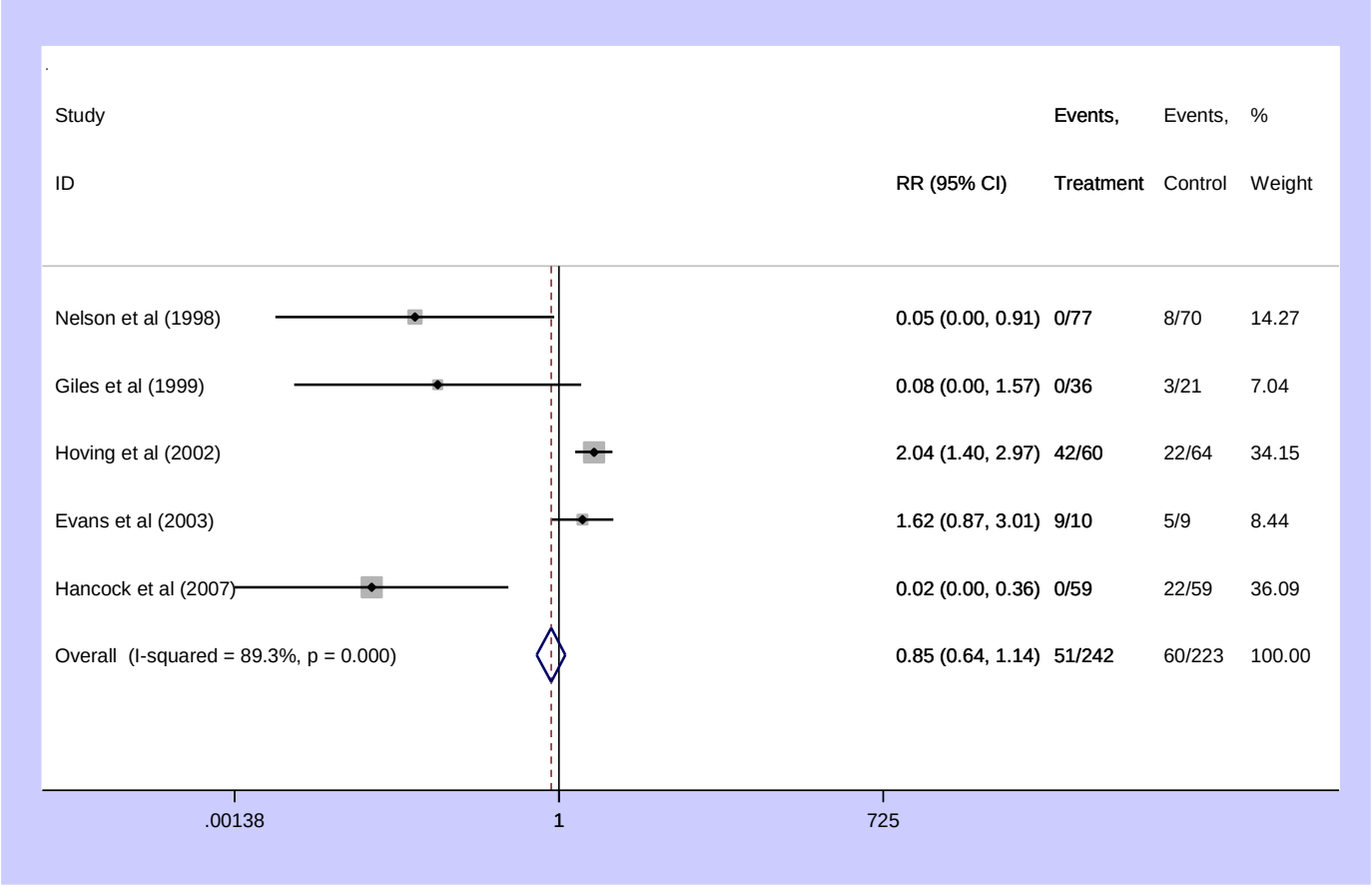
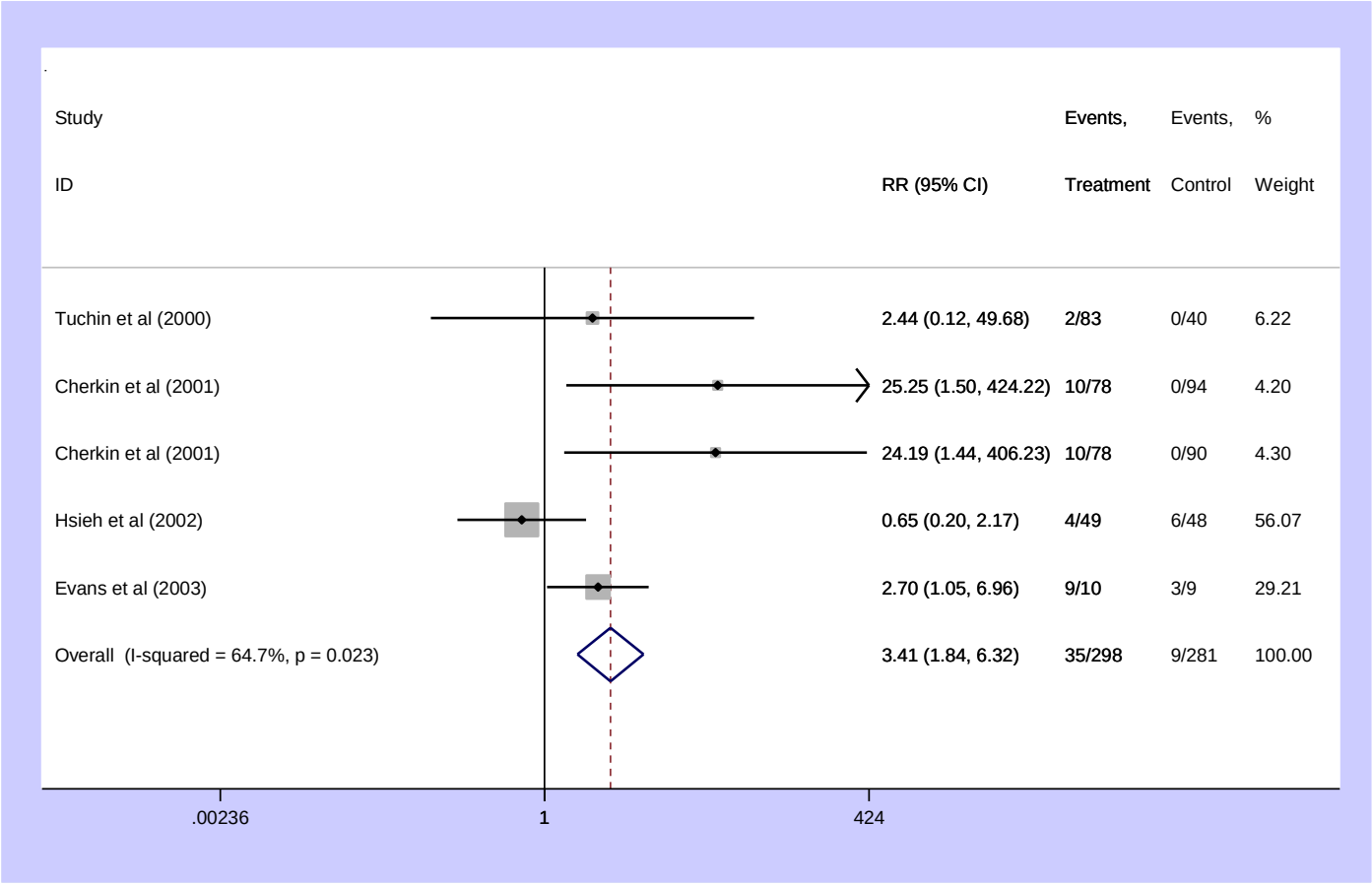


Figure 6 shows the relative risk of having an adverse event with manual therapy and other CAM therapies or passive approaches. The RCTs were quite diverse. Tuchin et al (2000) used detuned interferential (with a consultation), Cherkin et al (2001) acupuncture and self care, Evans et al (2003) self care and Hsieh et al (2002) backschool. The manual therapies included, massage (Cherkin et al 2001), chiropractic care (Evans et al 2003) and joint and spinal manipulation (Hsieh et al 2002, Tuchin et al 2000). RCT quality in this group was poor overall (range 32 – 66 /100). Figure 6 forest plot favours other CAM therapies and passive approaches, i.e. a significantly reduced risk of adverse events occurring with backschool, self care, detuned interferential and acupuncture.

Figure 6 RR for adverse events with manual therapy vs other CAM therapy



*****Interventions: Tuchin et al (2000), SM vs detuned interferential, Cherkin et al (2001) – massage vs acupuncture and self care respectively, Hsieh et al (2002) SM vs backschool, Evans et al (2003) chiropractic vs self care.

In addition to the above analyses we meta-analysed all the RCT data to explore the risk of adverse events occurring in the manual therapy arms of the trials compared to all the other arms in the trials. The statistic that illustrates the level of heterogeneity, the I-square value, was very high indicating that the meta-analysis to this extent was inappropriate. Additionally the wide confidence intervals

we obtained showed there was lack of power in the raw data, i.e. the patient numbers and adverse event outcomes were not large enough to give accurate estimates of risk.

Population Incidence

Detailed information about sources of estimates and data quality can be found in Appendices A and B. The data varies according to the number of manipulations or treatments administered over a defined period, estimates of the number of patients treated and the source of data reporting or diagnosing the adverse event. We extracted data about the estimated incidence of death with spinal manipulation, cervical artery complications with manipulation (table 8); neurological vascular and other major complications and manipulation (table 9) and other/minor/moderate incidences and manipulation (table 9).

Incidence rates for death and cervical artery complications with spinal manipulation

Three articles reported incidence rates for death and 13 reported incidence of cervical artery complications.

Table 8 Incidence of death and cervical artery complications data

Author (Evidence, Quality)	**Incidence rate**
Deaths	
Hurwitz (1996) (I Hi)	1 death: 3,333,333 cervical spine manipulations
Haneline (2003) (V Med)	0 deaths from cervical manipulation related ICADs: 3,606,870,000 cervical manipulation over one year in USA
Dabbs (1995) (V Lo)	1 death: 400,000 patients receiving cervical manipulation treatments over one year
Treatment-related cervical artery complications	
Anderson-Peacock (2005) (I Hi)	1 VAD: 1 million cervical manipulations
Hurwitz (1996) (I Hi)	1 VBA or serious complication: 1,000,000 cervical spine manipulations 1 major impairment : 1,666,666
Boyle (2008) (III Hi)	0.75 VBA strokes:100,000 person years (Ontario over 9 yrs) 0.86 VBA strokes:100,000 person years (Saskatchewan over11yrs)
*Cashley (2008)** *(III Hi)*	*1 stroke: 2,699 cervical manipulations* *1 stroke: 337 patients (background incidence only regardless of treatment, per annum)*
Rothwell (2001) (IIIMed)	1.3 VBAs:100,000 persons <45years within 1 week of chiropractic manipulation
Dupeyron (2003) (IV Hi)	2-6 VBAs plus other complications:100,000 cervical manipulations per year (1:25,000)
Haldeman (2002) (IV Hi)	1 stroke: 5,846,381 cervical manipulations in a 10 year period (1:584,638 per annum) 1 stroke: 1,430 practice years 1 stroke: 48 chiropractors would have a patient with a stroke after cervical SM during their careers
Klougart (1996a) (IV Med)	1 CVA: 1.3 million cervical spine treatment sessions 1 CVA: 0.9 million upper cervical treatment sessions
Klougart(1996b)(IVMed)	1 CVI: 120,000 cervical spine treatment sessions
Michaeli (1993)(IV Med)	1 CVA: 228,050 'procedures'
Carey (1993) (IV Lo)	1 CVA: 3,846,153 cervical manipulations (over 5 yrs)
Haneline (2003) (V Med)	1 ICAD: 601,145,000 cervical manipulations
Dabbs (1995) (V Lo)	0.5-2 stroke: 1 million cervical manipulations

Cervical artery complications include cervical artery dissections (CADs) vertebral artery accidents and incidents (VBAs and VBIs), internal carotid artery dissections (ICADs) and vascular related strokes and or transient ischaemic attacks (TIAs), all of which are major medical problems.

The range of data for the estimated incidence of serious cervical artery complications per cervical manipulations is between 1: 25,000 to 1: 601,145,000.

If we remove the two outliers, Dupeyron (2003) and Haneline (2003) and Michaeli (1993) who did not define 'procedures', the range per major cervical artery complication after spinal manipulation is 1:120,000 to 1:1,666,666 with a median of 1 serious cervical artery complication per 1,000,000 cervical manipulations (we selected and included the most homogenous data from Anderson-Peacock 2005, Hurwitz 1996, Klougart 1996 a and b and Dabbs 1995, table 8)

*Cashley's (2008) data is particularly interesting because it is based on an estimated risk of chiropractic patients having a stroke regardless of chiropractic treatment. The age profile of chiropractic patients were matched against national data (Scottish) and incidence estimated accordingly. This data is not included in our analysis as it is an estimated incidence based on a non manipulated population.

Incidence rates for major complications and manual therapy

Data were extracted about neurological, vascular (not specified as cervical artery dissections or strokes) and disc related complications. These complications were reported descriptively and constitute major adverse events using our Delphi criteria because they were either described as high intensity (unbearable), irreversible and/or serious. Nine articles reported data fitting this definition.

Table 9 Incidence data for neurological, vascular and other serious complications

Author (Evidence level, quality)	**Incidence data for neurological, vascular and other serious complications**
Coulter (1998) (I Lo)	6.4 serious neurological complications: 10,000,000 cervical manipulations 1 serious neurological complication (cauda equina): 100,000,000 lumbar manipulations
Ernst (2001) (I Med)	1 'serious adverse effect': 2,500 spinal manipulation treatments
Oliphant (2004)(IMed)	<1 disc herniation or cauda equina syndrome: 3.7 million lumbar manipulations
Senstad (1996) (II Hi)	1 unbearable side effect: 88 patients 1 unbearable side effect: 337 chiropractic treatments
Thiel (2007) (II Hi)	1 immediately occurring serious adverse event:10,000 cervical spine manipulation treatments 1 serious adverse event within 7 days: 100 cervical spine manipulations 6 'serious adverse events': 100,000 cervical spine consultations
Dvorak (1985) (IVMed)	1 major neurological deficit/complication: 41,500 cervical manipulations 1 severe neurological complication: 383,750 cervical manipulations
Dvorak (1993) (VI Med)	1 transient complication(disturbed consciousness, radicular symptoms):16,716 cervical manipulations over 1 yr 1 complication (increased pain, motor deficit or radiculopathy: 20,125 lumbar manipulations over 1 year 1 disc herniation: 38,013 lumbar manipulations over 1 year
Malone (2002) (IV Lo)	1 irreversible complication: 850 patients 1 irreversible complication: 8,500 cervical manipulations (using own study data) or 1 irreversible complication: 45,600 cervical manipulations (using other study estimates)
Dabbs (1995) (V Lo)	1 vascular complication: 100,000 patients treated with cervical manipulations
Author	**Other/minor/moderate complications**
Thiel (2007) (II Hi)	6 minor side effects with neurological involvement: 100,000 cervical spine manipulations 13-16 minor side effects with neurological involvement:1,000 treatment consultations to the cervical spine 4 headaches within 7 days: 100 treatment consultations to the cervical spine
Rivett (1997) (IV Hi)	1 minor transient complication: 1,756 manipulations
Margarey (2004) (IV Med)	1 adverse effect: 177.5 therapist weeks over 2 years 1 adverse effect: 50,000 cervical spine manipulations over 2 years 1 adverse effect: 180-184 therapist weeks for passive manual therapy to the cervical spine over 2 years 1 adverse effect:1.38 therapists over 2 years 168.5 adverse events: 1,000 practice years
Michaeli (1993) (VI Med)	1 complication: 3,020 cervical manipulation 1 complication: 38,137 thoracic or lumbar manipulations

Data for major adverse events, excluding arterial dissections, from cervical spinal manipulation or treatment ranged from 1:8,500 to 1:1,562,000 and for lumbar manipulations 1:20,125 to 1:100,000,000.

The definitions for the adverse events were not well described, but we have categorised them as serious and moderate adverse events using our Delphi study classification criteria. Lumbar manipulations with complications are reported by Coulter (1998), Dvorak (1993) and Oliphant (2004). The Coulter (1998) and Oliphant (2004) data was based on systematic reviews and Dvorak's (1985 and 1993) on survey data from manual therapists in Switzerland, all these were studies of medium to low quality. Senstad (1996) and Thiel (2007) conducted prospective surveys and define the adverse events in more detail in their articles. These were high quality studies specifically designed to explore risk and incidence. In both studies the manual treatment was administered by chiropractors who had the choice of using the activator instrument (a manipulation tool), however reported use of this was low (<5%) therefore the studies satisfied our inclusion criteria.

This data on major complications illustrates the diversity in reporting between studies and the poor definitions of adverse events making comparison and pooling of the data difficult. We have incidence rates for therapist weeks, manipulations, consultations and years of practice and different types of adverse events. There is little similarity between the datasets and no discernable emergent trends.

Quality of studies reporting incidence

The quality of data in Table 7 is mainly from high quality prospective cohort studies, both nominator and denominator figures give accurate prevalence data reflecting patient reports of adverse events, the data is not based on estimates. The evidence and quality rating are presented in the first column of each table. All the data is limited due to problems inherent with human recall, drop-outs and responder bias (therapist and clinician survey data).

6.4 Risk factors associated with manipulation and adverse events

The risk factors data presented here shows those factors that may predispose patients to the occurrence of an adverse event with manual therapy and the evidence for or against their occurrence after manual therapy (Tables 10 -25). The data was very diverse precluding any meta-analysis, a basic narrative summary is presented.

Likely factors associated with manual therapy and vascular complications include:

- upper cervical manipulation (2/2 studies)
- neck pain/stiffness prior to treatment (4/5 studies)
- seeing a manual therapist or primary care physician (3/4 studies)
- being female (3/4 studies)

Likely risk factors for reporting any adverse events post-manipulation include:

- first manual therapy treatment session (3/3 studies)
- being female (3/5 studies)
- regular medication use (1/1 study)

Possible risk factors for both vascular and non-vascular adverse events:

- rotation manipulation (3/4 studies)
- infection (1/1 study)

Inconclusive/insufficient data were found for the occurrence of adverse events after manual therapy, for prior:

- cardiovascular co-morbidity
- headache
- migraine
- oral contraception
- smoking

Those under 45 years may be more likely to see a manual therapist or primary care physician before a stroke than controls, and more likely to report an adverse event as a result of manual therapy than those over 45 years.

Hufnagel (1999) investigated 10 cases of stroke following cervical manipulation and found 'uneventful medical history, no or only mild vascular risk factors and no predisposing vascular lesions'. Thus patients at risk of stroke after manipulation may not be identified *a priori*.

There were no data about the following suggested risk factors with manual therapy:

- anticoagulant medication
- arterial insufficiency
- diabetes
- psychological disposition
- poorly/untrained manipulators
- homeocystine.

There were data about the occurrence of cervical artery dissections (CADs) and the above risk factors, but these studies did not focus on manual therapy or manipulation with these risk factors.

Author, type of study, evidence and quality	Detail	Data
Table 10 Age as a risk factor with manual therapy		
Senstad (1996a) Pros. Clinic survey (II Hi)	27-46 year olds more likely to report an adverse reaction than 47-64 year olds	60% (CI 95% 56-64) vs 49% (CI 95% 43-55)
Cagnie (2004) Pros. Coh. Study (II Hi)	Age not statistically significantly related to headaches post manipulation at 48 hrs	For every 1 year increase in age there is a 2.4% decrease in risk of headache
Cassidy (2008) Pop. case control (III Hi)	<45 year old patients 3 times more likely to visit a chiropractor or primary care physician before a stroke than controls	OR 2.8 (CI 95% 1.4-5.5) to visit a chiropractor OR 10.6 (CI 95% 3.5-32.8) to visit a primary care physician
Rothwell (2001) Nested case control (III Med)	Those <45 years with a VBA were more likely than controls to have visited a chiropractor within 1 week of their VBA (no significant association in those over 45years)	OR 5 (CI 95% 1.32 – 43.87)
Terret (1987) Retro case review(V Lo)	No age group at any significantly greater risk from vascular accident from cervical manipulation	
Table 11 Gender as a risk factor with manual therapy		
Barret (2000) Pros. Coh Study (III Hi)	No difference in reporting of adverse events between males and females (68 questionnaires)	No data
Cagnie (2004) Pros. Coh Study (II Hi)	Females more likely than males to report side effects post manipulation Females more likely to report headaches	OR 1.84 (CI 95% 1.3-2.7) OR 1.66 (no confidence interval reported)
Senstad (1996a) Pros. Clinic survey (II Hi)	Females more likely to report at least one side effect and recurrent side effects	One side effect 65% females (CI 95% : 61-68) vs 44% males (CI 95% : 40-48) Recurrent side effects 30% females (CI 95% : 28-32) vs 18% males (CI 95% 16-20)
Lebouef-Yde (1997) Pros. Qu'aire survey (III Med)	Females more likely than males to report adverse events	28% (26-30) vs 21% (18-24)
Oppenheim (2005) Record review (IV Hi)	Equal number of males and females with non-vascular complications following chiropractic spinal manipulation identified over a 6 year period	9 males vs 9 females
Reuter (2006) Retro. clinic survey (IV Med)	Patients admitted to a neurological department with VADs post chiropractic therapy to the neck over three years	24 females vs 12 males
Terrett (1987) Retro case review (V Lo)	No significant gender predilection from 107 case studies of vascular accidents	59 females vs 44 males (4 unknown)

Assendelft (1996) Lit review (V Lo)	VBAs reported more in females than males (165 reports)	84 vs 67 males (14 cases gender not reported)
Table 12 Hypertension as a risk factor with manual therapy		
Reuter (2006) Retro. clinic survey (IV Med)	From a sample of patients who had both manipulation and VAD there were more with cardiovascular risk factors	22 with cardiovascular risk factors / 36 without cardiovascular risk factors (61%)
Haldeman (2002b) Review case study cohort (V Med)	A history of hypertension with CVA	13% of sample
Table 13 Headaches pre-treatment as a risk factor with manual therapy		
Reuter (2006) Retro. clinic survey (IV Med)	From a sample of patients who had both manipulation and VAD there were less with tension type headaches as the main presenting complaint than without tension-type headaches	7 with headaches / 36 without headaches (19.4%)
Haldeman (2002a) Retro case review (V Med)	More CVAs occurred in those with history of head/neck disorders than those without a history of headaches/neck disorders	Head/neck disorders, 59 people of 64 with CVAs - 92%
Terret (1997) Retro case review (V Lo)	Some patients had history of headaches pre manipulation and stroke	Of 129 patients who had a stroke and a manipulation 16.3% (21 people) had headaches
Table 14 Infection as a risk factor with manual therapy		
Dittrich (2007) Case control study (IV Hi)	Infection <7 days prior to CAD, is almost significant risk factor, when combined with mechanical triggers significance is achieved	p=0.07 OR 3.5 (CI 95% 1.2-16.7)
Table 15 Location of manipulation as a risk factor with manual therapy		
Cagnie (2004) Pros. Coh. Study (II Hi)	Upper cervical SMs are more likely to give headaches, nausea and dizziness than lower cervical SMs. Upper cervical SMs are more likely to cause headache than lower cervical SMs Dizziness and nausea significantly more present after cervical SMs compared to thoracic and lumbar SMs	P=0.004 OR 3.17 (no confidence interval reported) Dizziness P=0.022 Nausea P=0.031
Klougart (1996)(part 2) Qu'aire survey (IV Med)	Upper cervical manipulations greater incidence than lower cervical SMsto cause CVI.	1:97,000 vs 1:370,000
Table 16 Migraines as a risk factor with manual therapy		
Cagnie (2004) Pros. Coh. Study (II Hi)	Migraine sufferers were statistically significantly more likely to get headaches post manipulation than non-migraine sufferers	P<0.001

Reuter (2006) Retro. clinic survey (IV Med)	Patients who had both manipulation and VAD there were less with a history of migraines than without a history of migraines	6 with migraines / 36 without migraines (16.7%)
Haldeman (2002a) Retro case review(V Med)	More CVAs occurred in those with history of migraines than those without the history	Migraines, 22 people of 64 people with CVAs) - 33%
Table 17 Neck pain/stiffness as a risk factor with manual therapy		
Dziewas (2003) Retro case review(IV Med)	Patients with vertebral artery dissections complained more often of neck pain, more frequently reported a preceding chiropractic manipulation and had a higher incidence of bilateral dissections than patients with carotid arterial dissections	20 patients were manipulated, 5 had carotid, 14 vertebral artery dissections, 1 both ($p<0.01$ for CAD vs VAD)
Dittrich (2007) Case control study (IV Med)	Neck pain statistically significantly more frequent in patients (<7 days) before onset of CAD	P=0.01
Smith (2003) Nested retro case control review (IV Med)	Patients more likely to have had neck or head pain preceding stoke or TIA than controls	Adjusted OR 3.76 (95% CI 1.3-11)
Reuter (2006) Retro. clinic survey (IV Med)	From a sample of patients who had both manipulation and VAD there were more with tension and pain to the neck muscles than without tension and pain in the neck muscles	24 with tension and pain / 36 with VADs (66%)
Terret (1997) Retro case review (V Lo)	Less than half of those who had a VBA stroke and a manipulation had prior neck pain	46.5% of 129 patients
Haldeman (2002a) Retro case review (V Med)	Nearly all strokes with a temporal association to cervical SM presented with a history of head and/or neck pain	92% (59/64)
Table 18 Number of areas treated as a risk factor with manual therapy		
Senstad (1996a) Pros. Clinic survey (II Hi)	Positive association between increases in reports of headache, fatigue and local discomfort and number of areas (1–3) treated in one treatment session	Headache 2% (one area treated) - 7% (3 areas treated) Fatigue 2% - 8% Local discomfort 15% - 24%
Table 19 Oral contraception as a risk factor with manual therapy		
Cagnie (2004) Pros coh.study(II Hi)	No statistically significant difference in reports of adverse events between users and non-users	
Reuter (2006) Retro. clinic survey(IV Med)	From a sample of patients who had both manipulation and VAD there were 24 females of whom almost equal numbers were/were not taking oral contraception	11 taking oral contraception / 24 females in total (45.8%)
Table 20 Regular use of medication as a risk factor with manual therapy		
Cagnie (2004)	Regular medication users were statistically significantly more likely	P=0.011

Pros. Coh. Study (III Hi)	to get headaches post manipulation than those who do not take medication regularly	
Table 21 Rotation manipulations as a risk factor with manual therapy		
Rubinstein (2008) Pros. Coh. Study (II Hi)	Rotation manipulation more likely to be associated with any type of adverse event after 1st and 3rd visit	1st visit OR 1.98 (CI 95% 1.16-3.39) 3rd visit OR 2.33 (CI 95% 1.34-4.08)
Dupeyron (2003) Qu'aire survey (IV Hi)	Association of VBAs with cervical rotatory manipulations	50% of sample with VBA had rotation manipulation. 96% occurred within 8 days and 53% within 24 hours of manipulation.
Klougart (1996) (part 2) Qu'aire survey (IV Med)	Rotation manipulation to the upper cervical spine has greater incidence of CVI than non-rotational procedures to the upper cervical spine	1:83,000 vs 1: 145,000
Michaeli (1993) Qu'aire survey (IV Med)	More cases of complications involved in rotation manipulations of the cervical spine	18/25
Table 22 Seeing a clinician as a risk factor with manual therapy		
Cassidy (2008) Pop. case control (II Hi)	Increase risk of having VB stroke if patient had seen either a chiropractor or primary care physician (PCP) with a headache. Those under 45 yrs with VBA more likely to have seen a chiropractor in last month than case controls	OR for Chiropractor 1.18 (1.02-1.37) OR for PCP 3.99 (2.88-5.53) Rate ratio 5.03 P=0.009
Rubinstein (2008) Pros. Coh. Study (II Hi)	Visiting a GP in 6 months before a chiropractic visit was protective of any musculoskeletal adverse event	OR 0.59 (95% CI 0.32-1.09) for increased neck pain and pain and/or stiffness at the treated area
Rothwell (2001) Nested case control study (III Med)	Patients with VBAs were more likely to have visited a chiropractor on >=3 occasions about their cervical spine within last month than controls Those <45 years with a VBA were more likely than controls to have visited a chiropractor within 1 week of their VBA (no significant association in those over 45years)	OR 3.09 (CI 95%1.15-8.29) bootstrap (0.99-12.10) OR 5 (CI 95% 1.32 – 43.87)
Smith (2003) Nested case control study (IV Med)	Patients with stroke or TIA more likely to have had spinal manipulation within 30 days than control group	Adjusted OR 6.62 (95% CI 1.4-30)
Table 23 Onset of adverse events with number of treatments as a risk factor with manual therapy		
Senstad (1996a) Pros. Coh. Study (III Hi)	Adverse reactions are more common after the first treatment	40% at first treatment vs 13% at 6th treatment
Senstad (1996b) Pros. Coh. Study (II Hi)	Adverse reactions are more common after the first treatment	87% commenced on first day of treatment
Leboeuf-Yde (1997) Pros. Coh.	Adverse reactions are more common after the first treatment	33% (29-37) occurred at first treatment vs 9% (2-16) after 6th

Study (II Med)		treatment
Table 24 Smoking as a risk factor with manual therapy		
Cagnie (2004) Pros. Coh. Study (II Hi)	Smokers registered significantly more headaches post manipulation than non-smokers	P=0.045
Haldeman (2002b) Case study review (V Med)	One quarter of a sample who had a CVA and a manipulation had a history of smoking	25% (16/64)
Terret (1997) Retro case review (V Lo)	Smoking does not appear to increase risk of vertebrobasilar stroke after spinal manipulative therapy	10/177 who had a VBA after manipulation were smokers
Table 25 Working status of patient as a risk factor with manual therapy		
Rubinstein (2008) Pros. Coh. Study (II Hi)	Borderline significance that those working are borderline/possibly/likely to have an adverse event than those seeking compensation, or sick-leave patients	Adjusted OR 2.88 (95% CI 0.87-9.47 or 0.96-8.66 depending on first or third visit data)

6.5 Nature and type of adverse events

The main table used for extraction of information about the nature and type of adverse events is given in Appendix F. We present data about the timing of onset of adverse events, the duration of adverse events, consequences of vascular accidents and fatalities associated with manual therapy treatment.

Onset of adverse events

Sixteen studies reported data about the onset of adverse events during or after treatment (table 26). The studies listed in italics are those reporting the onset of major adverse events (using our Delphi criteria). The italicised text indicates studies reporting major adverse events.

Table 26 Onset of adverse events

Author (Evidence, quality)	Subject of Study	Onset
Mild and moderate adverse events		
Hurwitz (1996) (I Hi)	Manipulation and Mobilisation of the Cervical Spine. Systematic Review	First symptoms: During therapy 13% (15/118) Within seconds of therapy 57% (67/118) Within 24 hours 22% (26/118) Later 8% (10/118) 70% of symptoms during therapy or within seconds 92% of symptoms within 24 hours
Vohra (2007 (I Hi)	A Systematic Review of AEs associated with Peadiatric SM	10/14 (71%) onset of adverse events within 24 hours
Barret and Breen (2000) (II Hi)	Adverse effects of Spinal Manipulation within 48 hours post treatment	Post treatment reactions at: one hour 28/68 (41%) one morning after 8/68 (12%) Two mornings after 0
Cagnie (2004) (II Hi)	Side effects of Spinal Manipulation after first visit (within 48 hours).	60.5% reactions started 4 hours or< 4 hours post manipulation.
Hurwitz (2004/5) (II Hi)	Chiropractic care of neck pain.	Onset 24or <24 hours = 171/212 (80.7%) 81% of symptoms began within 24 hours of treatment 30% reported at least 1 adverse event in the first 2 weeks
Rubinstein 2007/8 (II Hi)	Chiropractic care of neck pain.	56% at least one adverse event after any of first three treatments and 13% reported events to be severe.
Senstad (1996) (II Hi)	Side effects of Spinal Manipulative Therapy.	Same day 87% Immediate 14% < 60mins 42%
Senstad (1996) (II Hi)	Predictors of side effects to Spinal Manipulative Therapy.	9/14 (64%) episodes of "unbearable discomfort" occurred within first two treatment sessions. Adverse reactions after first treatment, 40% After 6th treatment, 13%
Senstad (1997) (II Hi)	Side effects of Spinal Manipulative Therapy.	<=10 minutes 198(17%) 10minutes-4 hours 556(47%) >4hours 373 (32%) Not stated 47(4%) 64% within 4 hours
Leboeuf-Yde 1997 (II Med)	Side effects of chiropractic treatment.	Same day 58% Next day 33% Later 4% Don't know 1% No response 4% 91% within 48 hours
Major adverse events*		
Klougart (Part 1) (1996) (IV Med)	Occurrence of CVA after manipulation to the neck	4/5 (80%) immediate 1/5 (20%) 10 minutes 100% of symptoms in 10 minutes.
Klougart (Part 2) (1996) (IV Med)	Occurrence of Cerebrovascular Incidents and treatment of the upper neck.	Immediately 13/22 (59%) < 1 hour 4/22 (18%) >24 hours 1/22 (5%) Undetermined 4/22 (18%) 77% of symptoms within one hour 82% of symptoms within 24hours
Reuter (2006)(IV Med)	Vertebral Artery Dissection post chiropractic neck manipulation.	Within session 14% (5) <60 mins 12% (4) 1-6hrs 14% (5) 6-12hrs 20% (7) 12-48hrs 5% (14) >48hrs 24% (9)

** major adverse events in this table are vascular complications as opposed to mild and moderate adverse events such as Neck symptoms, Radiating symptoms, Tiredness/fatigue, Headache, Dizziness/imbalance, Nausea/vomiting, Visual deficit, Hearing deficit, Limb weakness, Confusion/disorientation, Depression/Anxiety.*

The majority of non-vascular mild to moderate adverse events are likely to be evident within 48 hours of a treatment (Haldeman (2002) 94%, Hufnagel (1999) 100%, Rubinstein (2007/8) 72%,

Leboeuf -de (1997) 91%, Reuter (2006) 65%). Between 65% and 100% of all adverse events have an onset within 48 hours (mean 84%) . At 24 hours ~ 79% (range 55-83%) of adverse events have occurred.

Duration of adverse events

Nine studies reported data about the duration of non-CVA, mild to moderate adverse events (table 27). Various timescales were measured, the figures in bold in table 27 indicate duration of less than or equal to 24 hours.

Table 27 Duration of mild to moderate (non-CVA) adverse events post treatment

Author (Evidence, quality)	Subject of study	Duration of non-CVA related adverse events (mild to moderate adverse events)
Cagnie (2004) (II Hi)	Side effects of Spinal Manipulation after first visit (within 48 hours).	**64% of reactions did not last more than 24 hours** 19.4% of reactions lasted >48 hours
Hurwitz (2004/5) (II Hi)	Chiropractic care of neck pain.	>24hours 82/212 (38.7%) By implication **61% had symptoms resolving < 24hours**
Senstad (1996a) (II Hi)	Predictors of side effects to Spinal Manipulative Therapy.	< 4hours 23% <12hours 55% **< 24hours 83%** 24-48 hours 11% 48-72 hours 6%
Senstad (1997) (II Hi)	Side effects of Spinal Manipulative Therapy.	Reactions disappeared: During day of treatment 864 (74%) During day 2 183 (16%) During day 3 or later 81 (7%) Not stated 48 (4%) **74% disappeared within 24 hours** 90% disappeared within 48 hours
Thiel (20078) (II Hi)	Safety of Chiropractic Manipulation of the Cervical spine	Up to 7 days post treatment: Headaches - at worst 4/100 consultations. upper limb numbness/tingling -at worst 15/1000 consultations. fainting/dizziness/light headedness -at worst 13/1000 consultations.
Leboeuf-Yde (1997) (II Med)	Side effects of chiropractic treatment.	Few hours only 21% Up to 24 hours 34% Between 24-48 hours 19% >48 hours 19% Don't know 1% No response 6% **55% <=24 hours**
Adams (1998) (IV Med)	GP/public survey into adverse events of complementary and alternative medicine.	43 reported complications reported by 25/43 (19%) of users. 28 (65%) <1 week 15 (35%) >1 week
Egizii (2005) (IV Hi)	Spinal manipulation a survey of French medical physicians.	26 adverse events post spinal manipulation **17/26 (65%) < 24 hours** 9/26 (35%) > 24 hours
Michaeli (1993) (IV Med)	Complications of manipulative physiotherapy to cervical spine	Complications from cervical manipulation, lasting: <30minutes 1/25 (4%) 1-12 hours 5/25 (20%) 1-3 days 12/25 (48%) 1 week 5/25 (20%) 6-12 weeks 2/25 (8%) 2 years 0 (0%) Average recovery period 6.3 days. < 72 hours 18/25 (72%) Complications from cervical mobilization, lasting: <30minutes 12/48 (25%) 1-12 hours 24/48 (50%) 1-3 days 10/48 (21%) 1 week 1/48 (2%) 6-12 weeks 0/48 (0%) 2 years 1/48 (2%) <72 hours 46/48 (96%)

Six studies show that the majority of mild to moderate non-CVA related adverse events resolve within 24 hours (range 55% - 83%, mean 67%). We estimate that ~ one third of manual therapy patients may experience adverse events for a longer period of time, Michaeli (1993) reports that 96% resolve within 72 hours and Senstad (1996) reports 94% resolution for the same time period. A

smaller proportion may experience adverse events for longer periods.

Residual effects of adverse events

Table 28 shows the residual effects of CVA related adverse events.

Table 28 Residual symptoms of non-fatal CVAs

Author (Evidence, quality)	**Adverse event associated with manipulation**	**Outcome**
Dziewas (2003) (IV Med)	126 people with CAD, outcome at 6 months	70% excellent recovery 22 (17%) mild to moderate handicap 15 (12%) severe handicap 1 (0.8%) fatalities
Lee (1995) (IVMed)	Stroke patients at 3 months following onset of neurological complications	37% (21/57) had severe or moderate deficits
Klougart N et al. (1996) (IV Med)	Occurrence of **cerebrovascular incidents** after manipulation to the neck.	Resolution of adverse events: <1 hour 6/22 (27%) <24 hours 6/22 (27%) >24 hours 5/22 (23%) Undetermined 5/22 (23%) 54%<24 hours
Hufnagel (1999) (IV Lo)	Stroke following chiropractic manipulation of the cervical spine	50% (5/10) had severe or marked deficits at 4 year follow up
Assendelft (1996) (V Lo)	Patients with vertebrobasilar symptoms	29/165 (17.6%) died 86/165 (56%) residual handicap
Haldeman (2002) (V Med)	Patients post CVA	18% (8/44) had completely recovered one year 50% (22/44) experienced loss of coordination 32% (14/44) had speech/swallowing dysfunctions34% (15/44 had numbness 30 % (13/44) had visual disturbance
Terret 1987 (V Lo)	Vascular Accidents from Cervical Spine Manipulation a report on 107 published cases	26 fatalities 10 almost complete recovery 11 complete recovery 1 unknown but survived 30 years 7 unknown

Non-fatal cerebrovascular accidents appear to produce substantial morbidity. All studies reported exposure at some time point to manual therapy preceding the vascular accidents, in most studies we cannot specifically determine temporality or causality.

Table 29 Effect of manual therapy associated adverse events on daily activity

Author (Evidence, quality)	**Adverse event effect on 'activities of daily living'**	**Reported prevalence of effect in those with adverse reactions**
Hurwitz (2004 and 2005) (II Hi)	Impact 'a little' Impact 'a lot'	41% **19%**
Rubinstein (2007 and 2008) (II Hi)	Impact none or minor influence	85% after 2nd visit 81% after 4th visit Assume **15-19%** had more significant effect
Cagnie (2004) (II Hi)	Difficulty with daily living as a result of adverse events	**27%**
Leboeuf-Yde (1997) (II Med)	Discomfort as a results of treatment affected daily living	**9% 'a lot'** 26% 'somewhat' 57% 'not at all'
Senstad (1997) (II Hi)	Unable to perform daily activities due to reactions	**11%**

Bold indicates the data used to estimate a range of more significant effects on daily living in those experiencing adverse events, which ranges from 15%–27%.

Reported fatalities

Eight studies reported fatalities occurring post-manual therapy (table 30). However, Terret (1987), Assendelft (1996), Hurwitz (1996) and Vohra (2007) are reviews of the literature and therefore reported data is likely to be duplicated. The rest of the articles are retrospective reviews of either published cases or patient records concerning patients who have had a vascular incident post-manipulation.

Table 30 Number of fatalities reported post-manipulation or manual therapy care

Study (Evidence, quality)	Subject of Study	Number of fatalities reported
Hurwitz (1996) (I Hi)	Manipulation and Mobilisation of the Cervical Spine. Systematic Review	21 (reports from 1966)
Vohra (2007) (I Hi)	A Systematic Review of Adverse events associated with Pediatric Spinal Manipulation	3 reported since 1966. Indirect due to 'inappropriate care' i.e. delayed diagnoses of meningitis and embryonal rhabdomyosarcoma
Klougart (1996) (Part 1) (IV Med)	Occurrence of Cerebrovascular Accidents after manipulation to the neck.	1 (Denmark between 1978-1988)
Oppenheim (2005) (IV Hi)	Nonvascular complications following spinal manipulation.	3 (patients from a US neurosurgical practice between 1995 – 2001)
Reuter (2006) (IV Med)	Vertebral Artery Dissection post chiropractic neck manipulation.	1 (in 21 German university affiliated hospital neurology centers over 3 years)
Dziewas (2003) (IV Med)	Cervical Artery Dissection, a study of outcome in 126 patients	1 (one German hospital 1992 – 2001, it is unclear whether this patient had chiropractic care)
Assendelft (1996) (V Lo)	Complications of Spinal Manipulation a review of the literature	29 reported (details of search does not indicate a time frame, but does not go beyond 1993)
Terret (1987) (V Lo)	Vascular Accidents from Cervical Spine Manipulation a report on 107 published cases	26 (reported cases between 1934 and 1984)

6. 6 Systematic and literature reviews

There were seven systematic reviews assessing adverse events with manual therapy, and two assessing efficacy with information about risk of adverse events as component of the review. There were nine literature reviews about adverse events that varied in thoroughness and levels of data extraction. Table 31 shows a narrative extraction of data about the conclusions made in each review. The third column in this table indicates the level of evidence (see Section 5.5) and the quality of the articles.

Table 31 Summary of systematic and literature reviews

Author	Aim	Level Qual	Studies reviewed	Results of interest	Summary conclusion
Systematic reviews					
Anderson-Peacock, (2005)	To provide evidence about chiropractic manipulation for acute or chronic neck pain	I High	Treatment 182 AEs 230 Risk 79 Update 121	AEs not addressed in most studies. When reported majority were minor	Recommend heightened vigilance for: any treatments to the neck, minimum rotation and upper cervical SM
Ernst (2007)	Identify AEs of SM since 2001 -2007	I High	28 articles, 32 case reports. 64 retrospective case series, 2 prospective case series, 4 case control studies, 3 surveys	Most common serious AE reported was VADs. Mild AEs occur in 30% - 61% of patients post SM	SM frequently associated with AEs but incidence data unknown. Reconsider policy towards use of SM in interest of patient safety
Hurwitz (1996)	Assess evidence for efficacy and complications of cervical SM	I High	67 studies, 14 RCTs, 2 cohort studies, 14 case series, 37 case reports	Complication rate 5-10: 10 million cervical SMs	Complication rate small but possibility of adverse events needs consideration because of severe potential consequences
Rubinstein (2005)	To review pathogenesis of CAD	I High	31 case control studies examining 8 risk factors including trauma to neck (SM)	Association of trivial trauma i.e. neck manipulation with CAD, OR 3.8 95% CI 1.3 to 11	Strong association for risk factors with a genetic component and trivial trauma(i.e. cervical SM) but studies contain bias common in case control studies
Vohra (2007)	Analyses data about AEs and peadiatric SM	I High	13 studies, 2 RCTs, 11 observational studies	14 cases of direct AEs as a result of SM. 9 major, 2 moderate, 3 minor. Plus 20 cases of indirect AEs	Serious AEs may be associated with peadiatric SM. Need for prospective studies
Bronfort 2001	Assess efficacy of SM for chronic headache	I Med	9 trials reviewed reporting data on 683 participants	From pooled data. 5% withdrew due to complications and AEs after SM. 0 VBAs in any study reported	Recommends further rigorous research and follow up
Ernst (2001)	To summarise data from prospective investigations of SM AEs	I Med	5 studies met criteria up to 1998	Major adverse events not common but minor AEs 50% after treatments	Transient events are frequent, serious events probably rare but these are all based on estimates. More prospective studies needed
Oliphant (2004)	To provide qualitative review of risk of SM for lumbar disc herniation and severe AEs	I Med	8 Reviews 9 prospective/ retrospective surveys 2 surveys.	Risk estimate of SM worsening herniation and cauda equina in those with lumbar disc herniation <1:3.7mill	SM apparently safe therefore should stimulate increased use in conservative treatment of lumbar disc hernias
Coulter (1998)	To assess the appropriateness of SM	I Low	25 controlled trials of low back pain 67 studies for cervical SM	Low back pain, 1500 pooled participants, 0 complications reported. 110 cases of complications from cervical SM. Estimate 6.39 serious complications:10 million cervical SM and 1: 100 million lumbar SM	Risk of serious complications are very low and compares favourably to other therapies for same conditions

Author	Aim	Qual	Studies reviewed	Results of interest	Summary conclusion
Literature reviews					
Gross (2007)	Determine prevalence of risk factors associated with VAD after trauma and SM	V High	179 articles yielding 533 cases. 367 met final criteria for inclusion	Of the 367 VAD/Occlusion case studies, 160 (43%) were spontaneous, 115 (31%) assoc with SM, 58 (16%) with trivial trauma and 37 (10%) with major trauma	Data poor in literature so cannot answer research question
Haldeman (1999)	Assess literature about neck movement and VAD and VBA	V High	367 case reports.	160 spontaneous onset VADs, 115 after SM, 58 trivial trauma, 38 major trauma (3 both)	Data in the literature too poor to identify associations.
Haneline (2003)	To determine relationship between Chiropractic and CAD	V Med	13 Internal carotid artery dissections published.	Estimate > 7000 cases of ICAD per annum in the USA. Primary presentation neck pain and headache so likely to see a chiropractor not necessarily causal	No clear causal relationship between SM and ICAD and cases are scarce
Shekelle (1992).	Review use, complications and efficacy of SM for low back pain	V Med	25 RCTs reviewed	Pooled subjects from RCTs = 1500 SM patients 0 adverse events reported	Complication rates are unknown
Assendelft (1996)	Review literature about risk and complications of SM therapy	V Low	295 case reports: VBA 165, cerebral complications 13, disc herniation and cauda equina 61, & other 56. 3 surveys.	VBA outcomes of 165 cases: 29 Deaths, 86 residual handicap, completed recovery 44, unknown 6. No new incidence or risk data.	Difficult to estimate incidence. Possible under-reporting. VBAs difficult to prevent and treat. Avoid rotation SM. Risk information should be given to patients
Dabbs (1995).	To review literature to assess risk of death from stroke after SM	V Low	Not clearly stated	Some insurance data presented. Estimate rate of <1 stroke per 2 million cervical SM. 1 serious incident in 100,000cervical SM. Risk of death 1 per 400,000 patients treated	NSAIDs more risk to patient than SM
di Fabio (1999)	Review case reports to assess risk and benefit of SM	V Low	177 case reports of complications post SM	20% arterial dissection. 18% deaths. 70% complications attributed to chiropractors, rest other manual therapists.	Until more is known about effectiveness and risk of cervical SM **non-**thrust mobilization techniques should be considered as an alternative
Haneline (2005)	Review of etiology of CADs	V Low	606 CAD cases 321 CAD, 178 VAD	Of 606 CAD 371(61%) spontaneous, 178(29%) trivial or other trauma, 53(9%) SM	Risk of spontaneous dissection higher than SM and dissection

7. Discussion

7.1 Summary of results

The risk of major or serious adverse events following manual therapy was low, minor adverse events were frequent, but short-lived. Major adverse events were uncommon in both RCTs and prospective cohort studies. Our meta-analyses of RCT data was interesting as it showed that the risk of adverse events was higher in drug treatment groups and lower in passive treatment groups, such as self care, acupuncture and detuned interferential. These findings must be interpreted with caution because of the carefully selected populations used in trials and the issues involved with reporting adverse events in prospective cohort studies. Additionally we found defining adverse events in the context of manual therapy was difficult and that most population based incidence data are based on estimates, the actual risks are unknown.

7.2 Overall completeness of evidence and applicability

The literature search for this review found 90 articles (60 adverse events articles and 30 RCTs) recording some sort of data about adverse events. The data were often poorly and inconsistently reported with methodologies that lacked scientific rigour. The RCTs and the prospective cohort studies reviewed in this study presented the most reliable and robust data. The applicability of the varied and divergent evidence concerning incidence and risk is open to debate and warrants further discussion. There is a need for further research and better adverse events reporting in manual therapy efficacy trials and cohort studies.

Estimating incidence

We agree with the findings of others (Ernst 2005, Kerry 2008, Stevinson 2001) that incidence data is fraught with issues about accuracy due to methodological difficulties in collecting data. Incidence rates require accurate estimates of the number of patients visiting manual therapists, the number and type of treatments they are given and the number of occurrences of adverse events. Data collation of this type is difficult and quality depends not only on the sources of data but also on the validity of the data collection instruments. This review identified several methods of estimating incidence rates, each with particular limitations.

Adverse event incidence rates estimated from insurer data are often based on malpractice or negligence claims (Carey 1993). These data are often profession-specific and represents only those practitioners affiliated to the insurance provider. The applicability of these data to other manual

therapy professions is questionable. Personal insurance data can be used to estimate the number of practitioner visits from the cost of consultations claimed by the patients. However, these data can only reflect the insured fraction of the total consulting population. In the USA this may represent a large proportion of the consulting population but in the UK it would represent only those with sufficient funds to afford private insurance and care as opposed to state care. The national and international generalization of incidence rates derived from these data sets with inherent differences need to be taken into account when comparing the results from research studies undertaken in different countries.

Patient reports of adverse events appear to be sensitive to the various data collection tools used. For example methods allowing free responses, gave less reported adverse events, compared with more structured 'tick list' based reporting (Thiel (2007) vs Cagnie (2004)). Issues of confidentiality can influence patient and practitioner reporting, as can levels of patient satisfaction. Loss of patients in post treatment follow up can also distort true incidence figures (Thiel 2007 and 8).

Practitioner reports of adverse events such as those obtained in surveys, may be unduly influenced by practice regulations and business implications. There are potential differences between what people say they do compared to what they actually do (Adams 1998, Michaeli 1997) and the practitioner may be unaware of a missed diagnosis or adverse events as their patient may seek care elsewhere (Abbot 1998).

Journal reports of adverse events published as case studies are inadequate as a source for incidence estimation as they are generally subject to under reporting. In a survey of 323 neurologists (Stevinson 2001), 239 respondents reported 35 cases of stroke, acute subdural haemorrhage, myelopathy or cervical radiculopathy post-manipulation, none of which had been published. Klougart (1996 (part 1)) identified 5 cases of major adverse events from records, but only two had been published. Rivett and Milburn (1997) surveyed medical specialists and reported an underestimate of adverse-event related cases, as clinicians did not report data on those cases where they could not provide enough detail for the study.

Questionnaire surveys are also susceptible to recall bias and poor response rates. Dupeyron (2003) suggested that the incidence of VBAs as reported by medical specialists in a survey were 30 times higher than those in published case histories. Conversely, neurologists and vascular surgeons have reported quite high numbers of cases of vascular and neurological conditions, occurring after manual therapy treatments (in our review we identified a range of exposure between 16– 29%).

Additionally, patients may be seen by several clinicians in hospital environments and this can produce multiple reports related to a single patient (Dvorak 1993, Lee 1995, Rivett 1997). Haldeman (2002) surveyed neurologists and chiropractors found that exposure to cervical spine complications were three times more likely in neurologists, thus giving a skewed exposure to the risk of adverse events with manipulation.

Ernst (2001), Haneline (2003), Hurwitz (1996), Thiel (2007), Senstad (1996 b) have all concluded that although the risk of serious or major events with manual therapy is low, its presence is well documented and that the issue requires continued vigilance. The call for large prospective cohort studies has been championed by researchers and practitioners since the late 1990s (Ernst 2001, Rivett 1997, Assendelft 1996, Carey 1993). We identified 8 prospective cohort studies that explored the risk of adverse events that occurred as a result of spinal manipulation (Barrett 2000, Cagnie 2004, Senstad 1996 a&b, Garner 2007, Leboef-Yde 1997, Rubinstein 2007, Thiel 2007). In these studies, all of which involved the use of chiropractic technique, low risks of adverse events were reported despite a large number of spinal manipulations (0–1% of patients post-consultation had a serious adverse event and there were no cerebrovascular incidents or accidents). The follow up of drop-outs remains an issue with these studies, as do the methods of data collection, but they are more accurate than some of the estimates based on number of registered therapists or on the number of consultations and manipulations that may or may not have been administered (Carey 1993, Dvorak 1985 & 1993, Haldeman 2002 a&b, Dupeyron 2003, Boyle 2008).

Major adverse event incidence data can contribute to helping patients and practitioners to assess and understand risk, but in isolation this information is relatively meaningless. Additional data is needed about the risks of using alternative interventions and the potential benefits of other interventions that may be employed to treat the same problem.

7.3 Risk of vascular insult from spinal manipulation compared to other risks

This review identified a range of incidence rates for serious vascular insult after manipulation/ consultation. The range was wide due to the heterogeneity of the data. We selected the most homogenous data and estimated an incidence rate for vascular insult of around 1 per 1–1.6 million manipulations/consultations (using mean and median data). Using 1 vascular insult per 1 million manipulation/consultations as a reference, and based on an estimate that each patient receives between 5 and 10 manipulations per course of treatment, we can then deduce an incidence rate of 1 vascular insult per 50,000 patients or 100,000 cervical manipulations respectively.

The incidence rates for other types of vascular insufficiencies, including strokes, provide an interesting comparison. Cashley *et al* (2008) reports world standardised rates of first time stroke per 100,000 people in the general population. The rates for first time stroke in Italy are 114/100,000, Denmark 105/100,000, Australia 99/100,000, England 101/100,000 and Scotland 110/100,000. Cashley *et al* went on to infer the incidence of first time stroke in the general chiropractic population by using an age profile of chiropractic patients provided by the Chiropractic General Council and applying data from the Scottish Borders Stroke study. They estimated the non-causative background incidence of having a stroke in the UK general chiropractic population would be 1645 strokes per year, in an estimated pool of 554,975 chiropractic patients in a year, regardless of treatment (1:337 people or a one year incidence of 296 strokes per 100,000 chiropractic patients). These data suggest that the characteristics of chiropractic patients puts them at a higher risk of stroke than the general population.

The risk of spontaneous ICAD has been estimated between 0.5–3 cases per 100,000 of the general population per year (Schievink W. 2000). Based on the estimates for the incidence of a stroke or spontaneous dissection in the general population we can infer that the incidence for serious vascular injury in the manipulated population, if the age profile reflects that of the general population, would be similar or higher/more frequent than that for stroke or spontaneous dissection. We know that the age profile for those seeking manual therapy care is predominantly those between 35 and 50 years (Parsons et al. 2007) and that they may present with more 'at risk' characteristics such as neck pain and stiffness, headaches, dizziness etc. These data raise further concerns about the risks inherent in the manual therapy care seeking population regardless of therapy administered.

Risks related to pharmaceutical products and other intervention potentially used by manual therapy patients is equally as interesting as the risk of strokes. Our review of three RCTs comparing manual therapy with NSAIDs (Giles et al 1999), diclofenac (Hancock et al 2007) and amitriptyline (Nelson et al 1998) indicated that the risk of having an adverse event with the manual therapy (high velocity thrust) is less than the risk of taking the medication (Figure 5). Dabbs (1995) estimated a risk of death at 1 per 400,000 patients receiving a course of manipulative treatment per year (this data is based on a number of literature reviews but these papers are not specified), and death from using non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis over one year as 1 per 4,000 (0.04%) or 100-400 times greater than a patient receiving cervical manipulation treatment. Additional information from Oliphant (2004) compared the safety of lumbar manipulation with NSAIDs and surgery and concluded that manipulation was 37,000-148,000 times safer than

NSAIDs and 55,500-444,000 times safer than surgery for the treatment of lumbar disc herniation. Cauda equina syndrome was at least 7,400-37,000 times more likely to occur as a complication of surgery than spinal manipulation. Haneline's (2003) estimate using data gathered from a literature review, assessed the risk of death from being struck by an automobile as 1 per 20,000 people per year and death due to surgical procedures to the cervical spine 1:145. However, these studies (Dabbs 1995, Oliphant 2004 and Haneline 2003 & 5) were methodologically weak and rated medium to low in our quality appraisal.

Our meta-analysis comparing manual therapy to 'other' CAM therapies showed an increased risk of adverse events with manual therapy (Figure 6). The 'other' CAM therapies included self care, backschool, detuned interferential which included a consultation (so normal patient/clinician contact was sustained) and acupuncture. There is a possibility that the risk of adverse events with manual therapy vs no manual therapy is higher. However, 16 (about half) of our selected trials reported no adverse events in any arms of their studies. All these trials compared a form of manual therapy with either, another manual therapy, self care, sham therapies, other CAM therapies, education and/or GP care. The lack of adverse events in any of these treatment groups may counter the argument of increased risk with manual therapy.

Other studies looking at the aetiology of strokes have not reported any significant associations between strokes and spinal manipulation (Smith 2003, Dziewas 2003, Gross 2007, Haldeman 1999, Haneline 2003 and 2005). Rubinstein (2005) and Dittrich (2007), however, did find a positive and significant association between mild mechanical trauma (which included manipulation) and cervical artery dissection.

Our review included 22 papers reporting varied incidence data that indicated overall, there is a small risk of arterial dissections with manipulation. The profile and characteristics of those seeking care from manual therapists may differ from the general population and consequently increase their potential incidence rate of CVAs due to predisposing pre-treatment risk factors such as headache, neck pain and stiffness.

7.4 Risk factors associated with adverse events

It would be unwise to dismiss the incidence data associated with manipulation and arterial dissection because it is low and/or because the methods of data collection for estimates are flawed.

Regardless of these issues a risk exists that has implications for manual therapy practice.

The potential for causing an adverse event raises the importance of comprehensive training to ensure competent diagnoses and the appropriate selection and administration of therapy and vigilant case history taking to alert the clinician to possible risk factors.

This data in this review suggest that the presence of unusual neck pain and stiffness, previous mild mechanical traumas and upper cervical and rotational manoeuvres and manipulations may compound potential risks of adverse events. Risk factors associated with CADs are multifaceted (Rubinstein 2005, Haneline 2002, Haldeman 2002). Investigations show that risk factors associated with CAD, regardless of manual therapy are arterial diameter (Rubinstein 2005), unusual headaches, migraines and neck pain pre-treatment (Haldeman 2002, Haneline 2003, Rubinstein 2005), mild or trivial traumas that include manipulation (Dittrich 2006, Rubinstein 2005) and visiting a chiropractor (manual therapist) and or a primary care physician (General Practitioner) (Cassidy 2008). Dittrich et al. (2006) found that a recent infection was also statistically significantly more likely to be associated with CAD (OR 3.5, 95% CI 1.2-16.7) whilst cervical manipulation alone failed to reach significance. When data were combined for all mild mechanical traumas (including manipulation) in the preceding 24 hours to symptom onset there was a statistically significant difference in risk between CAD and non-CAD patients.

The risk of having minor to moderate (reversible) adverse events such as headache, dizziness, light-headedness and increased pain after manual therapy occurs in about 46% of treatments. Therapist vigilance is needed as some of the mild to moderate adverse events such as dizziness, dysphasia, altered consciousness, fainting and difficulty in swallowing may be dismissed when occurring in isolation but equally may be symptoms potentially associated with vertebro-basilar vulnerability (Margarey 2004).

To summarise, the data showed that the most likely factors associated with major adverse events, occurring after manual therapy are unusual neck pain/stiffness, having an upper cervical manipulation, and seeing a clinician in the preceding weeks (indicating patient concern about their condition rather than causality). Reports of adverse events are most likely to be made after the first treatments and by females.

7.5 Quality of data

The highest quality papers reviewed were prospective cohort studies. RCTs assessing manual therapy treatments ranged in quality, but in most cases adverse events were not the primary outcome measure, so the data reported on harms was generally poor. The events themselves were rarely described and few articles indicated the protocol for collecting adverse events data. Conversely, in the prospective cohort studies included in this review, adverse events reporting was the primary outcome measure and therefore produced better quality data. However, these studies have limitations as they may be subject to reporting bias by both patients and practitioners, and to patient selection bias. Additionally, patients may be treated concurrently by other health professionals and may well self-medicate. Large trials involving large numbers of practitioners are hard to manage and ensuring strict adherence to protocols can be difficult (Thiel 2008). In the absence of actual incidence data, prospective cohort studies and RCTs reporting adverse events as an outcome measure, provide the best estimates. The data reviewed cannot tell us whether causality is directly associated with the type of technique, inefficient application, poor diagnosis, co-morbidities or other influences. The timing of data collection can change the statistics reported, and worsening of symptoms may not necessarily be an adverse event. For example, Gibson (1999) reports increased symptoms following spinal manipulation (11%) at levels similar to placebo treatment (detuned diathermy) (12%), symptoms may represent normal in-treatment fluctuation and not be an effect of treatment (from Oliphant 2004). Without a control group and longer follow-up to monitor resolution, we do not know whether many adverse events reported are normal treatment variations or not.

Controlled study environments do not necessarily reflect the 'real world', and even pragmatic trials are subject to observer influence. Trials and cohort studies are regulated by strict protocols with carefully selected participants with few risk factors, thus possibly explaining the low reported incidence of major adverse events. Adverse events are not always as direct result of the manual therapy administered but due to poor diagnosis and application of the therapy (Egizii 2005).

7.6 Potential biases in the review

In this review we aimed to include studies that reported original data. This meant we excluded many literature and systematic reviews that contained purely narrative analysis and debate. We also excluded non-prospective effectiveness cohort studies and RCTs pre-1986, unless adverse events were the primary outcome measure. Potentially these articles could have contained more data about

adverse events, but on brief review the majority did not have adverse events as a secondary outcome measure of interest. We did not contact any of the authors regarding additional information and/or any relevant or unpublished data. We had sufficient literature and data available to us, and our inclusion criteria specified that our data had to be peer reviewed to increase appropriateness and quality of our data. We do not believe that this has unduly affected our findings as both positive and negative reports about manual therapy were reviewed.

In our main adverse events database just over half (33/60) of the research we reviewed was conducted by and/or, funded by chiropractors. There were 13 studies conducted by neurologists and medics, 8 studies conducted from a physiotherapy/physical therapy or physical medicine perspective, 6 had an academic research foundation and none were solely from an osteopathic perspective (Appendix G). The predominance of chiropractic focused studies may alienate some readers from considering the results presented here as relevant to the osteopathic profession. However the treatment approach being investigated in the majority of the studies was spinal manipulation. This technique is used across the three dominant manual therapy professions (chiropractic, osteopathy and musculoskeletal physiotherapy), and therefore we consider the results reasonably generalisable.

Since many of our conclusions are based on interpretation it is appropriate to consider our own biases. Two of the authors are registered osteopaths (DC, TM). One author (BM) is an employee of the European School of Osteopathy and the remaining author is an academic general practitioner who was one of the principal investigators of a major trial of manual therapy for low back pain. Two authors are active researchers in the field of low back pain and manual therapy (DC & MU). The study was funded by the GOsC who also have an interest in the outcomes. This report is based on the research team's interpretation of the data and does not necessarily reflect the views of the GOsC.

7.7 Agreement and disagreements with others

Ernst (2001) has been a strong advocate for urging caution about the use and safety of CAM, including manual therapies. We support his call for further research in this field and feel that this review goes some way towards aggregating and interpreting the varied data and thereby adds to the evidence about adverse events and manual therapy. We agree that mild adverse events occur commonly after manual therapy but we report that major adverse events are rare. We agree with Haneline (2005), Kerry (2008) and Rubinstein (2008) that major adverse events are more likely in

certain patient subgroups and that manual therapy techniques, particularly cervical manipulation should be administered with caution or not at all in those patients with signs and symptoms potentially associated with major adverse events such as CAD. We propose that, cervical spinal manipulation should be avoided in those patients presenting with combinations of unusual headaches, neck stiffness and pain, recent trauma and any history of cardiovascular insufficiency.

8. Conclusions and summary

The available data suggest that the risk of sustaining a major adverse event after osteopathic treatment is very low, in the order of 1: 8,500 to 1: 601,145,000 for all treatments and 1: 120,000 to 1:1,666,666 (excluding outliers) for manipulation of the cervical spine. The risk of an adverse event leading to persistent disability or death following a manipulation appears extremely rare, but the estimate, although grounded in data, is based on a variety of assumptions. These risks are in the same order as those that might be expected from a range of conventional medical treatments. However it would be unwise to dismiss the risk associated with manipulation and major adverse events, because it is low. Adverse events do occur, and this research has helped identify the risk factors associated with them. This may help manual therapists to understand and reduce the risk of them occurring. The profile and characteristics of people seeking manual therapy care make them a potentially vulnerable group. Thorough case history taking should alert manual therapists to the potential of cerebrovascular complications. The presence of unusual headaches, previous mild mechanical traumas and cardiovascular disease with neck pain and stiffness should alert manual therapists to proceed with caution if they choose to administer manual treatments to the cervical spine, especially rotation manipulation, for new patients for whom reaction to treatment is unknown.

Future research

Defining adverse events clearly is necessary to allow comparison of data for different treatment modalities generating equivalent adverse events. The rigorous reporting of adverse events in manual therapy trials is essential to allow for future pooling of data for meta-analysis.

Implications for practice

The patient and the practitioner can be advised that, 40 – 50% of first time patients experience minor to moderate adverse events after treatment and that most of these resolve within 48 hours and the risk of major adverse events with manual therapies is rare. The patient should advise the practitioner if they have had an unusual headache, neck pain and stiffness, weakness, recent trauma and any history of cardiovascular disease as these can influence the type of treatment that is administered to the patient. In such cases, spinal manipulation should be avoided.

Summary of key points

Patient / Practitioner Information Leaflet

About half of patients are likely to experience some minor to moderate short-lived adverse effects after manual therapy treatments.

Most minor and moderate adverse events resolve within 48 hours.

Research shows that adverse events are most likely to be reported after the first treatment received, and by females.

Risks of major adverse events, such as stroke with neck manipulation, are very low. Estimates suggest around 1 per 100,000 to 1,000,000 manipulations or 1 per 50,000 to 100,000 patients. To put this in perspective, the risk of having a stroke without a manipulation is around 100 strokes per 100,000 (or 1 per 1,000 people) in the general population in the UK over a one year period.

Upper neck and rotational manipulation and manoeuvres of the neck appear to be the treatment most commonly associated with an increased risk of cervical arterial injury.

Warning signs that potentially may indicate a higher risk of vascular injury and that contra-indicate manipulation are sudden onset of unusual or severe headache, pain and stiffness in the neck, previous mechanical trauma (including mild traumas) and a history of cardiovascular insufficiency.

The symptoms of vertebrobasilar dissections are neck pain and/or headaches that precipitate patients seeking care from either a manual therapist or their GP.

References

Abbot N.C., Hill M.et al. (1999). 'Uncovering Suspected Adverse Effects of Complementary and Alternative Medicine.' International Journal of Risk and Safety in Medicine. 11, 99-106.

Adams G., Sim J. et al. (1998). "A survey of UK manual therapists' practice of and attitudes towards manipulation and its complications." Physiotherapy Research International. 3(3): 206-27.

Anderson, R., Meeker W. C. et al. (1992). "A meta-analysis of clinical trials of spinal manipulation.[see comment]." Journal of Manipulative and Physiological Therapeutics. 15(3): 181-94.

Anderson-Peacock R, Eblouin J. S. et al. (2005). "Chiropractic clinical practice guideline: evidence-based treatment of adult neck pain not due to whiplash." Journal of the Canadian Chiropractic Association. 49(3): 158-209.

Assendelft, W. J., Bouter L. M. et al. (1996). "Complications of spinal manipulation: a comprehensive review of the literature.[see comment]." Journal of Family Practice. 42(5): 475-80.

Assendelft, W. J., Koes B. W. et al. (1996). "The effectiveness of chiropractic for treatment of low back pain: an update and attempt at statistical pooling." Journal of Manipulative and Physiological Therapeutics. 19(8): 499-507.

Assendelft, W. J., Morton S. C. et al. (2003). "Spinal manipulative therapy for low back pain. A meta-analysis of effectiveness relative to other therapies." Annals of Internal Medecine. 138(11): 871-81.

Assendelft, W. J., Morton S. C. et al. (2004). "Spinal manipulative therapy for low back pain." Cochrane Database Syst Rev 1.

Australian Government Department of Health and Aging. Adverse Drug Reactions Advisory Committee (ADRAC) www.tga.gov.au/adr/adrac (accessed 13/08/2008)

Axen I, Rosenbaum A. et al. (2002) 'Can Patient Reactions to the First Chiropractic Treatment Predict Early Favourable Treatment Outcome in Persistent Low Back Pain? Journal of Manipulative and Physiological Therapeutics, 25, 450-4.

Bannister L.H., Berry M.M. et al. Eds. (1995) Gray's Anatomy: The Anatomical Basis of Medicine and Surgery. 38th edn (New York: Churchill Livingstone. pp 1523-34.

Barrett, A. J., Breen A. C. et al. (2000). "Adverse effects of spinal manipulation." Journal of the Royal Society of Medicine 93(5): 258-9.

Beardmore H. (March 2008) 'The Context of Adverse Reactions and Consequences for Traditional Osteopathic Practice.' Osteopathy Today:14-6.

Beckerman, H., Bouter L. M. et al. (1993). "Efficacy of physiotherapy for musculoskeletal disorders: what can we learn from research?" Br J Gen Pract 43(367): 73-7.

Begg C, Cho M. et al. (1996) 'Improving the Quality of Reporting of Randomised Controlled Trails. The Consort Statement. Journal of the American Medical Association. 276 , 637-9.

Bisset, L., Paungmali A. et al. (2005). "A systematic review and meta-analysis of clinical trials on physical interventions for lateral epicondylalgia." British Journal of Sports Medicine. 39(7): 411-22.

Bjordal, J. M., Johnson M. I. et al. (2007). "Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials." BMC Musculoskeletal Disorders 8: 51.

Bland M.I. and Altman D.G. (2000) Editorials and Debate, Statistical notes – The odds ratio. British Medical Journal. May; 320: 1468

Boisaubert B., Brousse C. et al. (2004). "[Nonsurgical treatment of tennis elbow]." Annales de Readaptation et de Medecine Physique 47(6): 346-55.

Borchgrevink C., Leboeuf-Yde C. et al. "Predictors of Side Effects to Spinal Manipulative Therapy." Journal of Manipulative and Physiological Therapeutics. 1996 Sep;19(7):441-445.

Bove G., Nilsson N. et al. (1998). "Spinal manipulation in the treatment of episodic tension-type headache: a randomized controlled trial.[see comment]." Journal of the American Medical Association.280(18): 1576-9.

Boyle E., Cote P. et al. (2008). "Examining vertebrobasilar artery stroke in two Canadian provinces." Spine. 33(4 Suppl): S170-5.

Bradford-Hill A. (1965) 'The Environment and Disease: Association or Causation?' Proceedings of the Royal Society of Medicine. 295-300.

Bronfort G., Assendelft W. J. et al. (2001). "Efficacy of spinal manipulation for chronic headache: a systematic review." Journal of Manipulative and Physiological Therapeutics 24(7): 457-66.

Bronfort G., Evans R. et al. (2001). "A randomized clinical trial of exercise and spinal manipulation for patients with chronic neck pain." Spine 26(7): 788-97; discussion 798-9.

Bronfort G., Evans R. L. et al. "Distraction manipulation of the lumbar spine: a review of the literature." Journal of Manipulative and Physiological Therapeutics. 2005 May; 28(4):266-273.

Bronfort G., Haas M. et al. (2004). "Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis." Spine Journal: Official Journal of the North American Spine Society 4(3): 335-56.

Bronfort G., Nilsson N. et al. (2004). "Non-invasive physical treatments for chronic/recurrent

headache." Cochrane Database of Systematic Reviews(3): CD001878.

Brown M. J. (2001). "Prevalence of pathology seen on lumbar x-rays in patients over the age of 50 years." The British Journal of Chiropractic. 5(1-2): 23-30.

Cagnie B., Vinck E. et al. (2004). "How common are side effects of spinal manipulation and can these side effects be predicted?" Manual Therapy. 9(3): 151-6.

Carey P. F. (1995)"Cerebral Vascular Accidents: a Report on the Occurrences and the Incidence in a 5 Year Period in Canada." Journal of the Canadian Chiropractic Association. Jun:39(2):94-95.

Carey P. F. (1993) "A Report on the Occurrence of Cerebral Vascular Accidents in Chiropractic Practice." Journal of the Canadian Chiropractic Association. Jun:37(2):104-106.

Cashley M, C. M., McWilliam R, Steen L. (2008). "BISIMAN study: The background incidence if stroke in manipulation in the UK." Clinical Chiropractic.

Caspi O., Holexa J, (2005) 'Lack of Standardisation in Informed Consent in Complementary and Alternative Medicine.' Complementary Therapies in Medicine. 13, 123-30.

Cassidy, J. D., Boyle E. et al. (2008). "Risk of vertebrobasilar stroke and chiropractic care: results of a population-based case-control and case-crossover study." Spine. 33(4 Suppl): S176-83.

Cassidy J. D., Thiel H. W. et al. (1993). "Side posture manipulation for lumbar intervertebral disk herniation.[see comment]." Journal of Manipulative and Physiological Therapeutics. 16(2): 96-103.

Cawley N. (1997) 'A Critique of the Methodology of Research Studies Evaluating Massage.' European Journal of Cancer Care. 6, 23-31.

Cherkin D. C., Eisenberg D. et al. (2001). Randomized Trial Comparing Traditional Chinese Medical Acupuncture, Therapeutic Massage, and Self-care Education for Chronic Low Back Pain. Archives of Internal Medicine.161: 1081-1088.

Cherkin D. C., Sherman K. J. et al. (2003). "A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain." Annals of Internal Medicine 138(11): 898-906.

Chestnut J. L. (2004). "The stroke issue: paucity of valid data, plethora of unsubstantiated conjecture." Journal of Manipulative and Physiological Therapeutics. 27(5): 368-72.

Childs J. D., Flynn T. W. et al. (2006). "A perspective for considering the risks and benefits of spinal manipulation in patients with low back pain." Manual Therapy. 11(4): 316-20.

Christensen H. W., Hojgaard P. et al. (1998)."Vertebral Artery Flow and Spinal Manipulation: a Randomized, Controlled and Observer-Blinded Study." Journal of Manipulative and Physiological Therapeutics. Mar/Apr; 21(3):141-144.

Cleland J.A., Glynn P., et al. (2007).Short-term effects of thrust versus nonthrust

mobilisation/manipulation directed at the thoracic spine in patients with neck pain: a randomised controlled trial. Physical Therapy 87(4): 431-440.

Commission on Human Medicines (CHM) www.mhra.gov.uk (accessed 13/08/2008)

Conlin A., Bhogal S. et al. (2005). "Treatment of whiplash-associated disorders--part I: Non-invasive interventions." Pain Research Management. 10(1): 21-32.

Coulter I. (1996). "Manipulation and mobilisation of the cervical spine: the results of a literature survey and consensus panel." Journal of musculoskeletal Pain. 4(4): 113-123.

Cramer G., Budgell B. et al. (2006). "Basic science research related to chiropractic spinal adjusting: the state of the art and recommendations revisited." Journal of Manipulative and Physiological Therapeutics. 29(9): 726-61.

Croft A. C. (2003)"Manipulopathy: the Risk of Cervical Arterial Dissection, and Cerebrobascular Accident, and Chiropractic Manipulative Therapy." Journal of the American Chiropractic Association. Jul;40(7):22-25.

Crossley K., Bennell K. et al. (2001). "A systematic review of physical interventions for patellofemoral pain syndrome." Clinical Journal of Sports Medicine. 11(2): 103-10.

Dabbs V. and Lauretti W. J. (1995). "A risk assessment of cervical manipulation vs. NSAIDs for the treatment of neck pain." Journal of Manipulative and Physiological Therapeutics.18(8): 530-6.

Dagfinrud H., Kvien T. K. et al. (2005). "The Cochrane review of physiotherapy interventions for ankylosing spondylitis." Journal of Rheumatology. 32(10): 1899-906.

Dagfinrud H., Kvien T. K. et al. (2004). "Physiotherapy interventions for ankylosing spondylitis.[update of Cochrane Database Syst Rev. 2001;(4):CD002822; PMID: 11687163]." Cochrane Database of Systematic Reviews(4): CD002822.

Di Fabio R. (1999). "Manipulation of the cervical spine: risks and benefits." Physical Therapy. 79(1): 50-65.

Di Fabio R. P. (1992). "Efficacy of manual therapy." Physical Therapy.72 (12): 853-64.

Dittrich R., Rohsbach D. et al. (2006). “Mild Mechanical traumas Are possible Risk Factors for Cervical Artery Dissection.” Cerebrovascular Diseases. (23): 275-81.

Dvorak J., Loustalot D. et al. (1993). Frequency of complications of manipulation of the spine. A survey among the members of the Swiss Medical Society of Manual Medicine. European Spine Journal. (2): 136-9.

Dvorak J. And Orelli F.V. (1985). “How dangerous is manipulation to the cervical spine?” Manual Medicine. (2): 1-4.

Dupeyron A., Vautravers P. et al. (2003). "[Complications following vertebral manipulation-a survey of French region physicians]." Annales de Readaptation et de Medecine Physique. 46(1): 33-40.

Dziewas R., Konrad C. et al. (2003). "Cervical artery dissection--clinical features, risk factors, therapy and outcome in 126 patients.[see comment]." Journal of Neurology. 250(10): 1179-84.

Eck J. C., Circolone N. J. et al. (2000). "The use of spinal manipulation in the treatment of low back pain: a review of goals, patient selection, techniques, and risks." Journal of Orthopaedic Science. 5(4): 411-7.

Egizii G., Dupeyron A. et al. (2005). "[Spinal manipulation: survey of French medical physicians who graduated with the national diploma of osteopathy from Strasbourg University].[see comment]." Annales de Readaptation et de Medecine Physique 48(8): 623-31.

Ernst E. (2001). "Prospective Investigations into the Safety of Spinal Manipulation." Journal of Pain and Symptom Management. 21(3): 238-242.

Ernst, E. (2002). "Manipulation of the cervical spine: a systematic review of case reports of serious adverse events, 1995-2001." Medical Journal of Australia. 176(8): 376-80.

Ernst E. (2003). "Serious adverse effects of unconventional therapies for children and adolescents: a systematic review of recent evidence." European Journal of Pediatrics. 162(2): 72-80.

Ernst E. (2007). "Adverse effects of spinal manipulation: a systematic review." Journal of the Royal Society of Medicine. 100(7): 330-338.

Ernst E., Canter P. H. et al. (2006). "A systematic review of systematic reviews of spinal manipulation.[see comment]." Journal of the Royal Society of Medicine. 99(4): 192-6.

Ernst E. (1999). "Massage therapy for low back pain: a systematic review." Journal of Pain and Symptom Management. 17(1): 65-9.

Ernst E. (2000). "Does spinal manipulation have specific treatment effects?" Family Practice. 17(6): 554-6.

Ernst E. (2001). "Life-threatening complications of spinal manipulation.[see comment]." Stroke. 32(3): 809-10.

Ernst E. (2001). "Prospective investigations into the safety of spinal manipulation." Journal of Pain and Symptom Management. 21(3): 238-42.

Ernst E. (2002). "Manipulation of the cervical spine: a systematic review of case reports of serious adverse events, 1995-2001.[see comment]." Medical Journal of Australia. 176(8): 376-80.

Ernst E. (2003). "Chiropractic manipulation for non-spinal pain--a systematic review." New Zealand Medical Journal. 116(1179): U539.

Ernst E. (2003). "Chiropractic spinal manipulation for back pain." British Journal of Sports Medicine. 37(3): 195-6; discussion 196.

Ernst E. (2003). "Chiropractic spinal manipulation for neck pain: a systematic review.[comment]." Journal of Pain. 4(8): 417-21.

Ernst E. (2003). "The safety of massage therapy." Rheumatology. 42(9): 1101-6.

Ernst E. (2005). "Ophthalmological adverse effects of (chiropractic) upper spinal manipulation: evidence from recent case reports." Acta Ophthalmologica Scandinavica. 83(5): 581-5.

Ernst E., Harkness E. et al. (2001). "Spinal manipulation: a systematic review of sham-controlled, double-blind, randomized clinical trials.[see comment]." Journal of Pain and Symptom Management. 22(4): 879-89.

Evans R., Bronfort G. et al. (2003). "A pilot study for a randomized clinical trial assessing chiropractic care, medical care, and self-care education for acute and sub-acute neck pain patients." Journal of Manipulative and Physiological Therapeutics. 26(7): 403-411.

Ezzo J., Haraldsson B. G. et al. (2007). "Massage for mechanical neck disorders - A systematic review." Spine. 32(3): 353-362.

Fast A., Zinicola D.F. et al. (1987) 'Vertebral Artery Damage Complicating Cervical Manipulation.' Spine. 12, 840-2.

Ferreira M. L., Ferreira P. H. et al. (2002). "Does spinal manipulative therapy help people with chronic low back pain?[see comment]." Australian Journal of Physiotherapy. 48(4): 277-84.

Ferreira M. L., Ferreira P. H. et al. (2007). "Comparison of general exercise, motor control exercise and spinal manipulative therapy for chronic low back pain: A randomized trial." Pain. 131(1-2): 31-7.

'Foster vs Thornton. (1934). Medicolegal Abstract. Malpractice: Death Resulting from Chiropractic Treatment for Headache.' Journal of the American Medical Association. 103, 1260.

Fritzell P, Hagg O. et al, (2001) 'Swedish Lumbar Spine Study Group. A Multicentre Randomised Controlled Trial from the Swedish Lumbar Spine Study Group.' Spine. 26, 2512-34.

Frumkin LR, Balou RW, (1990) 'Wallenberg's Syndrome Following Neck Manipulation. Neurology. 40, 611-5.

Furlan A. D., Brosseau L. et al. (2002). "Massage for low back pain.[update of Cochrane Database Syst Rev. 2000;(4):CD001929; PMID: 11034734]." Cochrane Database of Systematic Reviews(2): CD001929.

Furlan A. D., Brosseau L. et al. (2002). "Massage for low-back pain: a systematic review within the

framework of the Cochrane Collaboration Back Review Group. Spine.27(17): 1896-910.

Garner M. J., Aker P. et al. (2007). "Chiropractic care of musculoskeletal disorders in a unique population within Canadian community health centers." Journal of Manipulative and Physiological Therapeutics. 30(3): 165-70.

Gemmell H. and Miller P. (2006). Comparative effectiveness of manipulation, mobilisation and the Activator instrument in treatment of non-specific neck pain: a systematic review. Chiropractic and Osteopathy.14: 7.

General Osteopathic Council, 'Code of Practice.' (2005).

Gibson J., Grant I., Waddell G. (1999). The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. Spine. 24: 1820 -32

Giesen J. M., Center D. B. et al. (1989). "An evaluation of chiropractic manipulation as a treatment of hyperactivity in children." Journal of Manipulative and Physiological Therapeutics. 12(5): 353-63.

Giles L. G., Muller R. et al. (1999). "Chronic spinal pain syndromes: a clinical pilot trial comparing acupuncture, a nonsteroidal anti-inflammatory drug, and spinal manipulation.[see comment]." Journal of Manipulative and Physiological Therapeutics. 22(6): 376-81.

Giles L. G., Muller R. et al. (2003). "Chronic spinal pain: a randomized clinical trial comparing medication, acupuncture, and spinal manipulation.[see comment]." Spine. 28(14): 1490-502; discussion 1502-3.

Grant K. E. (2003). "Massage safety: injuries reported in Medline relating to the practice of therapeutic massage--1965-2003." Journal of Bodywork and Movement Therapies. 7(4): 207-212.

Greenberg R.S. et al. (2001). Medical Epidemiology. 4th edition. Lange Medical Books/McGraw Hill. London.

Greenly L. W. (1992). "Vertebro-Basilar Accidents: Danger or an Acceptable Risk? Part 1--Incidence and Assessment." Chiropractic Technique. May;4(2):68-72.

Greenly L. W. (1992). "Vertebro-Basilar Accidents: Danger or an Acceptable Risk? Part 2--Conditions and Action Steps." Chiropractic Technique. Aug;4(3):115-116.

Grier A. R. (2004). "Adverse reactions to chiropractic treatment and their effects on satisfaction and clinical outcomes among patients enrolled in the UCLA neck pain study." Journal of Manipulative and Physiological Therapeutics. 27(6): 430-430.

Grieve G.P. (1994). 'Incidents and Accidents of Manipulation and Allied Techniques', in Grieves Modern Manual Therapy. The Vertebral Column., Ed. by Palastanga N, Boyling JD.Edinburgh: Churchill Livingstone. 673-92.

Grimshaw J, Eccles M. (1998) Evidence Based Practice in Primary Care. Eds Silagy C. and Haines A. BMJ Books, London

Gross A. R., Aker P. D. et al. (1996). "Manual therapy in the treatment of neck pain." Rheumatic Diseases Clinics of North America. 22(3): 579-98.

Gross A. R., C. Goldsmith J. L. et al. (2007). "Conservative management of mechanical neck disorders: a systematic review." Journal of Rheumatology. 34(5): 1083-102.

Gross A. R., Hoving J. L. et al. (2004). "A Cochrane review of manipulation and mobilization for mechanical neck disorders." Spine. 29(14): 1541-8.

Gross A. R., J. Hoving J. L. et al. (2007). "Manipulation and mobilisation for mechanical neck disorders (Review)." Cochrane Database of Systematic Reviews: Issue 4 Cochrane library.

Gross A. R., Kay T. et al. (2002). "Manual therapy for mechanical neck disorders: a systematic review." Manual Therapy 7(3): 131-149.

Gross A. R., Kay T. M. et al. (2002). "Clinical practice guideline on the use of manipulation or mobilization in the treatment of adults with mechanical neck disorders." Manual Therapy. 7(4): 193-205.

Haas M., Goldberg B. et al. (2004). "A practice-based study of patients with acute and chronic low back pain attending primary care and chiropractic physicians: two-week to 48-month follow-up." Journal of Manipulative and Physiological Therapeutics. 27(3): 160-9.

Hakkinen A., Salo P. et al. (2007). "Effect of manual therapy and stretching on neck muscle strength and mobility in chronic neck pain." Journal of Rehabilitative Medicine. 39(7): 575-9.

Haldeman S., Carey P. et al. (2002c). "Clinical perceptions of the risk of vertebral artery dissection after cervical manipulation: the effect of referral bias." Spine Journal: Official Journal of the North American Spine Society. 2(5): 334-42.

Haldeman S., Kohlbeck F. J. et al. (1999). "Risk factors and precipitating neck movements causing vertebrobasilar artery dissection after cervical trauma and spinal manipulation." Spine.24(8): 785-94.

Haldeman S., Kohlbeck F. J. et al. (2002a). "Stroke, cerebral artery dissection, and cervical spine manipulation therapy." Journal of Neurology. 249(8): 1098-104.

Haldeman S., Kohlbeck F. J. et al. (2002b). "Unpredictability of cerebrovascular ischemia associated with cervical spine manipulation therapy: a review of sixty-four cases after cervical spine manipulation" Spine. 27(1): 49-55.

Haldeman S., Rubinstein S. M. et al. (1992). "Cauda equina syndrome in patients undergoing manipulation of the lumbar spine." Spine. 17(12): 1469-73.

Hancock M. J., Maher C. G. et al. (2007). "Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial." Lancet. 370(9599): 1638-43.

Haneline M., Triano J. et al. (2005). "Cervical artery dissection. A comparison of highly dynamic mechanisms: manipulation versus motor vehicle collision." Journal of Manipulative and Physiological Therapeutics. 28(1): 57-63.

Haneline M. T., Croft V. et al. (2003). "Association of internal carotid artery dissection and chiropractic manipulation." Neurologist. 9(1): 35-44.

Haneline M. T., Lewkovich G. N. et al. (2005). "An analysis of the etiology of cervical artery dissections: 1994 to 2003." Journal of Manipulative and Physiological Therapeutics. 28(8): 617-22.

Harding J. E., Miles et al. (1998). "Chest physiotherapy may be associated with brain damage in extremely premature infants." Journal of Pediatrics. 132(3 Pt 1): 440-4.

Harris P., Rees R. (2000) 'The Prevalence of Complementary and Alternative Medicine Use among the General Population: A Systematic Review of the Literature.' Complementary Therapies in Medicine. 8, 88-96.

Hawk C., Khorsan R. et al. (2007). "Chiropractic care for non-musculoskeletal conditions: a systematic review with implications for whole systems research.[see comment]." Journal of Alternative and Complementary Medicine. 13(5): 491-512.

Hawk C., Long C. R. et al. (2005). "A randomized trial investigating a chiropractic manual placebo: a novel design using standardized forces in the delivery of active and control treatments." Journal of Alternative and Complementary Medicine 11(1): 109-17.

Hawk C., Rupert R. L. et al. (2006). "Comparison of bioenergetic synchronization technique and customary chiropractic care for older adults with chronic musculoskeletal pain." Journal of Manipulative and Physiological Therapeutics. 29(7): 540-9.

Hay E. M., Mullis R. et al. (2005). "Comparison of physical treatments versus a brief pain-management programme for back pain in primary care: a randomised clinical trial in physiotherapy practice." Lancet. 365(9476): 2024-30.

Haynes M.J. (1996) 'Doppler Studies Comparing the Effects of Cervical Rotation and Lateral Flexion on Vertebral Artery Blood Flow.' Journal of Manipulative and Physiological Therapeutics. 19, 378-84.

Hering C. Materia Medica of American Provings. ed. by Esrey WP (Michigan: Scholarly Publishing Office, University of Michigan, (2006).

Hoeksma H. L., Dekker J. et al. (2004). "Comparison of manual therapy and exercise therapy in osteoarthritis of the hip: a randomized clinical trial." Arthritis and Rheumatism. 51(5): 722-9.

Hondras M. A, Linde K. et al. (2005). "Manual therapy for asthma.[update of Cochrane Database Syst Rev. 2002;(4):CD001002; PMID: 12519548]." Cochrane Database of Systematic Reviews (2): CD001002.

Hondras M. A., Long C. R. et al. (1999). "Spinal manipulative therapy versus a low force mimic maneuver for women with primary dysmenorrhea: a randomized, observer-blinded, clinical trial." Pain. 81(1-2): 105-14.

Hoving J. L., de Vet H. C. et al. (2006). "Manual therapy, physical therapy, or continued care by the general practitioner for patients with neck pain: long-term results from a pragmatic randomized clinical trial." Clinical Journal of Pain. 22(4): 370-7.

Hoving J. L., Koes B. W. et al. (2002). "Manual therapy, physical therapy, or continued care by a general practitioner for patients with neck pain. A randomized, controlled trial.[see comment][summary for patients in Ann Intern Med. 2002 May 21;136(10):I36; PMID: 12020157]." Annals of Internal Medicine. 136(10): 713-22.

Hsieh,C.Y., Adams A. H. et al. (2002). "Effectiveness of four conservative treatments for sub-acute low back pain: a randomized clinical trial." Spine. 27(11): 1142-8.

Hufnagel A., Hammers A. et al. (1999). "Stroke following chiropractic manipulation of the cervical spine." Journal of Neurology. 246(8): 683-8.

Hurley L., Yardley K. et al. (2002). "A survey to examine attitudes and patterns of practice of physiotherapists who perform cervical spine manipulation." Manual Therapy. 7(1): 10-8.

Hurwitz E. L., Aker P. D. et al. (1996). "Manipulation and mobilization of the cervical spine - A systematic review of the literature." Spine. 21(15): 1746-1759.

Hurwitz E. L., Morgenstern H. et al. (2002). "A randomized trial of medical care with and without physical therapy and chiropractic care with and without physical modalities for patients with low back pain: 6-month follow-up outcomes from the UCLA low back pain study." Spine. 27(20): 2193-204.

Hurwitz E. L., Morgenstern H. et al. (2002). "Second Prize: The effectiveness of physical modalities among patients with low back pain randomized to chiropractic care: findings from the UCLA low back pain study." Journal of Manipulative and Physiological Therapeutics. 25(1): 10-20.

Hurwitz E. L., Morgenstern H. et al. (2002). "A randomized trial of chiropractic manipulation and mobilization for patients with neck pain: clinical outcomes from the UCLA neck-pain study.[see comment]." American Journal of Public Health. 92(10): 1634-41.

Hurwitz E. L., Morgenstern H. et al. (2006). "A randomized trial of chiropractic and medical care for patients with low back pain: eighteen-month follow-up outcomes from the UCLA low back pain study." Spine. 31(6): 611-21.

Hurwitz E. L., Morgenstern H. et al. (2004). "Adverse reactions to chiropractic treatment and their effects on satisfaction and clinical outcomes among patients enrolled in the UCLA Neck Pain Study." Journal of Manipulative and Physiological Therapeutics. 27(1): 16-25.

Hurwitz E. L., Morgenstern H. et al. (2005). "Frequency and clinical predictors of adverse reactions to chiropractic care in the UCLA neck pain study." Spine.30(13): 1477-84.

Institute for Safe Medication Practices (ISMP) www. ismp.org (accessed 13/08/2008)

Ioannidis JPA, Evans SJW. et al. (2004), 'Better Reporting of Harms in Randomised Trials: An Extension of the Consort Statement. Annals of Internal Medicine. 141(10). 781-8.

Ioannidis JPA. (2006) 'Adverse Events: The More You Search the More You Find.' Annals of Internal Medicine. 144, 298-9.

Jarski ,R. W., Loniewski E. G. et al. (2000). "The effectiveness of osteopathic manipulative treatment as complementary therapy following surgery: a prospective, match-controlled outcome study." Alternative Therapies in Health and Medicine. 6(5): 77-81.

Jull G., Trott P. et al. (2002). "A randomized controlled trial of exercise and manipulative therapy for cervicogenic headache." Spine. 27(17): 1835-43.

Kalamir A., Pollard H., et al. (2007). "Manual therapy for temporomandibular disorders: A review of the literature." Journal of Bodywork and Movement Therapies. 11(1): 84-90.

Kawchuk G.N., Jhangri G.S, et al. (2008) 'The Relation Between the Spatial Distribution of Vertebral Artery Compromise and Exposure to Cervical Manipulation.' Journal of Neurology. 255. 371-77.

Kerry R., Taylor AJ. et al. 'Cervical Arterial Dysfunction and Manual Therapy: A Critical Literature Review to Inform Professional Practice.' Manual Therapy, In press.

Klougart N., Leboeuf-Yde C. et al. (1996). "Safety in chiropractic practice, Part I; The occurrence of cerebrovascular accidents after manipulation to the neck in Denmark from 1978-1988." Journal of Manipulative and Physiological Therapeutics.19(6): 371-7.

Klougart N., Leboeuf-Yde C. et al. (1996). "Safety in chiropractic practice. Part II: Treatment to the upper neck and the rate of cerebrovascular incidents." Journal of Manipulative and Physiological Therapeutics. 19(9): 563-9.

Koes B. W., Assendelft W. J. et al. (1991). "Spinal manipulation and mobilisation for back and neck pain: a blinded review.[see comment]." BMJ 303(6813): 1298-303.

Koes B. W., Assendelft W. J. et al. (1996). "Spinal manipulation for low back pain. An updated systematic review of randomized clinical trials." Spine 21(24): 2860-71; discussion 2872-3.

Koes B. W., Bouter L. M. et al. (1995). "Methodological quality of randomized clinical trials on

treatment efficacy in low back pain." Spine. 20(2): 228-35.

Kohlbeck F. J., Haldeman S. et al. (2005). "Supplemental care with medication-assisted manipulation versus spinal manipulation therapy alone for patients with chronic low back pain." Journal of Manipulative and Physiological Therapeutics. 28(4): 245-52.

Korthals-de Bos I. B., Hoving J. L. et al. (2003). "Cost effectiveness of physiotherapy, manual therapy, and general practitioner care for neck pain: economic evaluation alongside a randomised controlled trial.[see comment]." British Medical Journal. 326(7395): 911.

Lauretti W. (1999)"What Are the Risks of Chiropractic Neck Adjustments?" Journal of the American Chiropractic Association. Sept;36(9):42-44.

Le Roux D. (1999). "Assessment of vertebrobasilar artery insufficiency: a clinical audit and literature review." The British Journal of Chiropractic. 3(1): 16-20.

Leboeuf-Yde C., Axen I. et al. (1999). "The types and frequencies of improved non-musculoskeletal symptoms reported after chiropractic spinal manipulative therapy." Journal of Manipulative and Physiological Therapeutics. 22(9): 559-64.

Leboeuf-Yde C., Gronstvedt A. et al. (2005). "The Nordic back pain subpopulation program: a 1-year prospective multicenter study of outcomes of persistent low-back pain in chiropractic patients." Journal of Manipulative and Physiological Therapeutics. 28(2): 90-6.

Leboeuf-Yde C., Hennius et al. (1997). "Side effects of chiropractic treatment: a prospective study." Journal of Manipulative and Physiological Therapeutics. 20(8): 511-5.

Leboeuf-Yde C., Senstad O. et al. (1996) 'Side-Effects of Chiropractic Spinal Manipulation: Types Frequency, Discomfort and Course.' Scandinavian Journal of Primary Health Care. 14, 50-3.

Leboeuf-Yde C., Pedersen E. N. et al. (2005). "Self-reported non-musculoskeletal responses to chiropractic intervention: a multination survey.[see comment]." Journal of Manipulative and Physiological Therapeutics 28(5): 294-302; discussion 365-6.

Leboeuf-Yde C., Klougart N. et al. (1996) 'Safety in Chiropractic Practice. Part II: Treatment to the Upper Neck and the Rate of Cerebrovascular Incidents.' Journal of Manipulative and Physiological Therapeutics. 19, 563-9.

Leboeuf Yde C., Hennius B. et al. (1997) 'Side Effects of Chiropractic Treatment: A Prospective Study. Journal of Manipulative and Physiological Therapeutics. 20, 511-5.

Lee K. P., Carlini W.G. et al. (1995). "Neurologic complications following chiropractic manipulation: a survey of California neurologists." Neurology. 45(6): 1213-5.

Lenssinck M. L., Damen L., et al. (2004). "The effectiveness of physiotherapy and manipulation in patients with tension-type headache: a systematic review." Pain .112(3): 381-8.

Lewis, M. and Johnson M. I. (2006). "The clinical effectiveness of therapeutic massage for musculoskeletal pain: a systematic review." Physiotherapy. 92(3): 146-158.

Lewkovich G. N., Haneline M. T. (2004) "Identification of internal carotid artery dissection in chiropractic practice." Journal of the Canadian Chiropractic Association. Sept; 48(3):206-210.

Licciardone J.,Gamber R., et al. (2002). "Patient satisfaction and clinical outcomes associated with osteopathic manipulative treatment." Journal of the American Osteopathic Association. 102(1): 13-20.

Licciardone J. C., Brimhall A. K. et al. (2005). "Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials." BMC Musculoskeletal Disorders 6: 43.

Licht P.B., Christiansen H.W. and et al. (1998) 'Triplex Ultrasound of Vertebral Artery Flow During Cervical Rotation. ' Journal of Manipulative and Physiological Therapeutics. 21, 27-31.

Licht P.B., Christiansen H. et al. (1998) 'Vertebral Artery Flow and Spinal Manipulation: A Randomised, Controlled and Observer Blinded Study. ' Journal of Manipulative and Physiological Therapeutics.21 (3).141-4.

Lindlhar H. (1926) Philosophy of Natural Therapeutics. 6th Ed Chicago: The Lindlahr Publishing Company.

Lisi A. J.,. Holmes E. J, et al. (2005). "High-Velocity Low-Amplitude Spinal Manipulation for Symptomatic Lumbar Disk Disease: A Systematic Review of the Literature." Journal of Manipulative and Physiological Therapeutics 28(6): 429-442.

Livingston M. C. (1971). "Spinal manipulation causing injury. A three-year study." Clinical Orthopaedics and Related Research. 81: 82-6.

Magerey M.E., Rebbeck T. et al. (2004). “Pre-manipulative testing of the cervical spine review, revision and new clinical guidelines.” Manual Therapy. (9):95-108.

Malone D. G., Baldwin N. G., et al. (2002). "Complications of cervical spine manipulation therapy: 5-year retrospective study in a single-group practice. [See comment]." Neurosurgical Focus. 13(6): ecp1.

Mascalchi M., Bianchi M. C. et al. (1997). "MRI and MR angiography of vertebral artery dissection." Neuroradiology. 39(5): 329-40.

Medlicott M. S., Harris S. R. et al. (2006). "A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder.[see comment]." Physical Therapy. 86(7): 955-73.

Mehalic T., Farhat S. M. et al. (1974). "Vertebral artery injury from chiropractic manipulation of the neck." Surgical Neurology. 2(2): 125-9.

Michaeli A. (1993). “Reported occurrence and nature of complications following manipulative physiotherapy in South Africa.” 39(4): 309-15.

Milburn P, Rivett D.A. (1997) 'Complications Arising from Spinal Manipulative Therapy in New Zealand.' Physiotherapy. 83, 626-32.

Mior S. (2001). "Manipulation and mobilization in the treatment of chronic pain." Clinical Journal of Pain 17(4 Suppl): S70-6.

Mohseni-Bandpei MA, Stephenson R, et al. (1998). "Spinal manipulation in the treatment of low back pain: a review of the literature with particular emphasis on randomized controlled trials." Physical Therapy. Reviews. Dec 3(4): 185-194.

Monaco G.P, and Smith G. (2002) 'Informed Consent in Complementary and Alternative Medicine: Current Status and Future Needs.' Seminars in Oncology. 29, 601-8.

Myers M.G, and Cairns J.A. (1987) 'The Consent Form as a Possible Cause of Side Effects.' Clinical Pharmacological Therapy.42, 250-3.

Nelson C. F., Bronfort G., et al. (1998). "The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache." Journal of Manipulative and Physiological Therapeutics. 21(8): 511-9.

Nicolakis P., Burak E. C. et al. (2001). "An investigation of the effectiveness of exercise and manual therapy in treating symptoms of TMJ osteoarthritis." Cranio 19(1): 26-32.

Noll D. R., Degenhardt B. F. et al. (2004). "Effectiveness of a sham protocol and adverse effects in a clinical trial of osteopathic manipulative treatment in nursing home patients." Journal of the American Osteopathic Association. 104(3): 107-13.

Oger J. (1964). "COMPLICATIONS OF VERTEBRAL MANIPULATION.]." Journal Belge de Medecine Physique et de Rhumatologie - Belgisch Tijdschrift voor Fysische Geneeskunde en Reumatologie 19: 56-78.

Oliphant D.(2004). "Safety of spinal manipulation in the treatment of lumbar disk herniations: a systematic review and risk assessment." Journal of Manipulative and Physiological Therapeutics. 27(3): 197-210.

Oppenheim J. S., Spitzer D. E. et al. (2005). "Nonvascular complications following spinal manipulation.[see comment]." Spine Journal: Official Journal of the North American Spine Society. 5(6): 660-7.

'Osteopaths Act. Chapter 21.' ed. by Office of Public Sector Information Her Majesty's Stationary

Office. London. 1993.

Ottenbacher K. and R. P. DiFabio (1985). "Efficacy of spinal manipulation/mobilization therapy. A meta-analysis." Spine. 10(9): 833-7.

Parsons S.et al (2007). 'Prevalence and comparative troublesomeness by age of pain in different body locations amongst those reporting chronic pain', Family Practice. 24 308 - 316 (0263-2136).

Plaugher G., Long C. R. et al. (2002). "Practice-based randomized controlled-comparison clinical trial of chiropractic adjustments and brief massage treatment at sites of subluxation in subjects with essential hypertension: pilot study." Journal of Manipulative and Physiological Therapeutics. 25(4): 221-39.

Powell (1993). "A risk/benefit analysis of spinal manipulation therapy for relief of lumbar or cervical pain." Neurosurgery. 33(1): 73-78 (discussion pp78-9).

Proctor M. L., Hing W. et al. (2006). "Spinal manipulation for primary and secondary dysmenorrhoea.[update of Cochrane Database Syst Rev. 2004;(3):CD002119; PMID: 15266463]." Cochrane Database of Systematic Reviews 3: CD002119.

Refshauge K. M., Parry S. et al. (2002). "Professional responsibility in relation to cervical spine manipulation.[see comment]." Australian Journal of Physiotherapy. 48(3): 171-9; discussion 180-5

Reuter U., Hamling M. et al. (2006). "Vertebral artery dissections after chiropractic neck manipulation in Germany over three years." Journal of Neurology. 253(6): 724-30.

Rivett D.A, 'Adverse Effects of Cervical Manipulative Therapy.' in Grieve's Modern Manual Therapy. The Vertebral Column., ed. by Boyling JD and Jull GA 2004.Churchill Livingstone. London. 533-49.

Roberts J.B, (1907) 'Fracture Dislocation of the Atlas without Symptoms of Spinal Cord Injury.' Annals of Surgery. 45. 632-5.

Romano M. and Negrini S. (2008). "Manual therapy as a conservative treatment for adolescent idiopathic scoliosis: a systematic review." Scoliosis 3: 2.

Rosner A. (2007). "Adverse events in the manipulation of pediatric patients: flaws in a systematic review.[comment]." Pediatrics. 119(6): 1261-4; author reply 1266-7.

Rothwell D. M., Bondy S. J. et al. (2001). "Chiropractic manipulation and stroke: a population-based case-control study.[see comment]." Stroke. 32(5): 1054-60.

Rubinstein S. M., Leboeuf-Yde C. et al. (2008). "Predictors of adverse events following chiropractic care for patients with neck pain." Journal of Manipulative and Physiological Therapeutics.31(2): 94-103.

Rubinstein S. M., Leboeuf-Yde C. et al. (2007). "The benefits outweigh the risks for patients undergoing chiropractic care for neck pain: a prospective, multicenter, cohort study." Journal of Manipulative and Physiological Therapeutics. 30(6): 408-18.

Santilli V., Beghi E. et al. (2006). "Chiropractic manipulation in the treatment of acute back pain and sciatica with disc protrusion: a randomized double-blind clinical trial of active and simulated spinal manipulations." Spine Journal: Official Journal of the North American Spine Society .6(2): 131-7.

Sawyer C. E., Evans R. L. et al. (1999). "A feasibility study of chiropractic spinal manipulation versus sham spinal manipulation for chronic otitis media with effusion in children." Journal of Manipulative and Physiological Therapeutics. 22(5): 292-8.

Schievinck W. (2000). "The treatment of spontaneous ICAD and vertebral artery dissection." Current opinion in cardiology. 15: 316-321.

Schiller L. (2001). "Effectiveness of spinal manipulative therapy in the treatment of mechanical thoracic spine pain: a pilot randomized clinical trial.[see comment]." Journal of Manipulative and Physiological Therapeutics. 24(6): 394-401.

Schmitt H. P. (1978). "[Manual therapy in the region of the cervical spine. Manual therapy of the cervical spine and its dangers: ruptures and occlusions of the vertebral artery]." ZFA (Stuttgart) 54(8): 467-74.

Senstad O., Leboeuf-Yde C. et al. (1996). "Predictors of side effects to spinal manipulative therapy." Journal of Manipulative and Physiological Therapeutics.19(7): 441-5.

Senstad O., Leboeuf-Yde C. et al. (1997). "Frequency and characteristics of side effects of spinal manipulative therapy." Spine. 22(4): 435-40; discussion 440-1.

Senstad O., Leboeuf-Yde C. et al. (1996). "Side-effects of chiropractic spinal manipulation: types, frequency, discomfort and course." Scandinavian Journal of Primary Health Care. 14(1): 50-3.

Shekelle P. G., Adams A. H. et al. (1992). "Spinal manipulation for low-back pain.[see comment]." Annals of Internal Medicine. 117(7): 590-8.

Shekelle P. G. and Coulter I. (1997). "Cervical spine manipulation: summary report of a systematic review of the literature and a multidisciplinary expert panel." Journal of Spinal Disorders. 10(3): 223-8.

Skargren E. I., Carlsson P. G. et al. (1998). "One-year follow-up comparison of the cost and effectiveness of chiropractic and physiotherapy as primary management for back pain. Subgroup analysis, recurrence, and additional health care utilization." Spine. 23(17): 1875-83; discussion 1884.

Skargren E. I., Oberg B. E. et al. (1997). "Cost and effectiveness analysis of chiropractic and physiotherapy treatment for low back and neck pain. Six-month follow-up." Spine. 22(18): 2167-77.

Smith W. S., Johnston S. C. et al. (2003). "Spinal manipulative therapy is an independent risk factor for vertebral artery dissection.[see comment]." Neurology. 60(9): 1424-8.

Snelling N. J. (2006). "Spinal Manipulation in patients with disc herniation: A critical review of risk and benefit." International Journal of Osteopathic Medicine. 9(3): 77-84.

Stevinson C., Ernst E., et al. (2002). "Risks associated with spinal manipulation." American Journal of Medicine. 112(7): 566-71.

Stevinson C, Honan W, Ernst E, (2001) 'Neurological Complications of Cervical Spine Manipulation. Journal of the Royal society of Medicine. March 107-10

Strunk R. G. and Hondras M. A. (2008). "A feasibility study assessing manual therapies to different regions of the spine for patients with subacute or chronic neck pain." Journal of Chiropractic Medicine. 7(1): 1-8.

'The Herxheimer Reaction-Feeling Worse before FeelingBetter.(2008)<http://www.tbyil.com/herxeimer.htm> [Accessed 13/08 2008].

Terrett A. G. "Vertebrobasilar Stroke after Spinal Manipulation Therapy." Advanced Chiropractic. 1997 ;4:383-415.

Terrett A. G. (1988). "Vascular Accidents from Cervical Spine Manipulation: Report on 107 Cases." Journal of Chiropractic. 25(4): 63-72.

Terret A.G. (1987). Vascular Accidents from Cervical Spine Manipulation: The Mechanisms.' Journal of the Australian Chiropractic Association. 17, 131-44.

Thiel H. and Bolton J. (2006). "The reporting of patient safety incidents—first experiences with the chiropractic reporting and learning system (CRLS): A pilot study." Clinical Chiropractic. 9(3): 139-149.

Thiel H. W., Bolton J. E. et al. (2007). "Safety of chiropractic manipulation of the cervical spine: a prospective national survey." Spine. 32(21): 2375-8.

Toole J., and Tucker S. (1960) 'Influence of Head Position Upon Cerebral Circulation: Studies on Blood Flow in Cadavers.' Archives of Neurology, 2, 616-23.

Tuchin P. J., Pollard H. et al. (2000). "A randomized controlled trial of chiropractic spinal manipulative therapy for migraine.[see comment]." Journal of Manipulative and Physiological Therapeutics 23(2): 91-5.

UK BEAM Trial Team. (2004). "United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care." British Medical Journal 329(7479): 1377-1381.

United States Food and Drug Administration (FDA) www.fda.gov (accessed 13/08/2008)

van Tulder M. W., Koes B. et al. (2006). "Outcome of non-invasive treatment modalities on back pain: an evidence-based review." European Spine Journal. 15 Suppl 1: S64-81.

van Tulder M. W., Koes B. W. et al. (1997). "Conservative treatment of acute and chronic nonspecific low back pain. A systematic review of randomized controlled trials of the most common interventions.[see comment]." Spine. 22(18): 2128-56.

Vernon H., Humphreys K. et al. (2007). "Chronic mechanical neck pain in adults treated by manual therapy: a systematic review of change scores in randomized clinical trials.[erratum appears in Journal of Manipulative and Physiological Therapeutics. 2007 Jul;30(6):473-8]." Journal of Manipulative & Physiological Therapeutics 30(3): 215-27.

Vernon H., McDermaid C. S., et al. (1999). "Systematic review of randomized clinical trials of complementary/alternative therapies in the treatment of tension-type and cervicogenic headache." Complementary Therapy Medicine. 7(3): 142-55.

Vernon H., Steiman I., et al. (1986). "Efficacy of spinal manipulation/mobilization: a meta-analysis." Spine. 11(9): 973-4.

Vernon H. (2003). "The effectiveness of spinal manipulation for the treatment of headache disorders: a systematic review of randomized clinical trials.[comment]." Cephalalgia 23(6): 479-80; author reply 480-1.

Vernon H. T., Humphreys B. K., et al. (2005). "A systematic review of conservative treatments for acute neck pain not due to whiplash." Journal of Manipulative and Physiological Therapeutics. 28(6): 443-8.

Vicenzino B., Paungmali A. et al. (2001). "Specific manipulative therapy treatment for chronic lateral epicondylalgia produces uniquely characteristic hypoalgesia." Manual Therapy. 6(4): 205-12.

Vick D. A., C. McKay, et al. (1996). "The safety of manipulative treatment: review of the literature from 1925 to 1993." Journal of the American Osteopathic Association. 96(2): 113-5.

Vohra S., Johnston B. C. et al. (2007). "Adverse events associated with pediatric spinal manipulation: a systematic review.[see comment][erratum appears in Pediatrics. 2007 Apr;119(4):867]." Pediatrics 119(1): e275-83.

Weintraub M, and Khoury A. (1995) 'Critical Neck Position as an Independent Risk Factor for Posterior Circulation Stroke. A Magnetic Resonance Angiographic Analysis.' Journal of

Neuroimaging. 5, 16-22.

Wiberg J. M., Nordsteen J. et al. (1999). "The short-term effect of spinal manipulation in the treatment of infantile colic: a randomized controlled clinical trial with a blinded observer.[see comment]." Journal of Manipulative and Physiological Therapeutics 22(8): 517-22.

Williams N. H., Hendry M. et al. (2007). "Psychological response in spinal manipulation (PRISM): a systematic review of psychological outcomes in randomised controlled trials." Complementary Therapies in Medicine. 15(4): 271-83.

Williams N. H., Wilkinson C. et al. (2003). "Randomized osteopathic manipulation study (ROMANS): pragmatic trial for spinal pain in primary care." Family Practice. 20(6): 662-9.

World Health Organisation. 'Prevalence of Use of Complementary/Alternative Medicine: A Systematic Review.' WHO Bulletin, 72 (2000), 252-7.

World Health Organization www.who.int/en (accessed 13/08/2008)

Appendix A: Delphi Paper

DEFINING ADVERSE EVENTS IN MANUAL THERAPIES: A MODIFIED DELPHI CONSENSUS STUDY

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DEFINING ADVERSE EVENTS IN MANUAL THERAPIES: A MODIFIED DELPHI CONSENSUS STUDY

Abstract

A pragmatic agreed definition of adverse events in manual therapy is required to explore incidence and prevalence. We aimed to identify and describe such adverse events and seek a consensus definition.

A focus group identified issues surrounding the definition of adverse events and generated the content for a questionnaire. This questionnaire was used to conduct a modified Delphi consensus survey with an expert panel (n=50). Consensus was defined as >74% agreement. Three consensus rounds were executed.

There was a 50% response rate for round one, 62% for round two and 55% for round three. A layered pragmatic definition was agreed:

- **'Major' adverse events** are medium to long term, moderate to severe and unacceptable, they normally require further treatment and are serious and distressing;
- **'Moderate' adverse events** are as 'major' adverse events but only moderate in severity; and
- **'Mild' and 'not adverse' adverse events** are short term and mild, non-serious, the patient's function remains intact, and they are transient/reversible; no treatment alterations are required because the consequences are short term and contained.

We concluded that classifying adverse events was difficult without context or detail. Classification may be improved by using the taxonomy and descriptions suggested in this study.

Introduction

The incidence of adverse events from manual therapy is of considerable interest to manual therapists and to the general public. Good quality data are sparse, with scientific debate about incidence of adverse events foundering on differences in opinion as to what constitutes a therapy-related adverse event rather than the incidence itself. Defining therapy-related adverse events in manual therapy is difficult as they occur in many guises, contexts and settings. They can range in severity and impact; also, patient and practitioner views and expectations about what constitutes an important adverse event may differ. The literature about manual therapy-related adverse events is dominated by studies about manipulation (Kerry 2008, Stevinson 2002); specifically, high velocity thrust techniques used on the cervical spine and consequential cervical artery dissections – vertebral and internal carotid arteries, vertebrobasilar accidents and strokes (Dittrich 2007, Haneline 2004, Kawchuk 2008) . There is, however, a large spectrum of adverse events that can occur with varying degrees of severity and duration, from transient muscle aches to bruising to fracture.

The World Health Organisation Adverse Reaction Team (WHO-ART) and the pharmaceutical industry have each been considering the definition of adverse events for decades and have clearer definitions than many other organisations (Leape and Abookire 2003). In addition, adverse events, reactions, harm, safety and side effects are defined and used in the revised and extended 2003 CONSORT statement (Ioannidis 2004) for reporting clinical trial data. Whilst these definitions and guidelines are useful to the manual therapy professions, they are not entirely applicable as it is often difficult to assign causality, or to measure the 'dose' of a manual therapy and, therefore, to describe signs and symptoms in the context of an adverse event.

Malone et al (2002) defined an adverse 'effect' as any detrimental result of a treatment; a 'reaction' as a slight or clinically insignificant short lived symptom and an 'incident' as an unexpected event resulting in serious impairment, injury or fatality or an irreversible complication. Thiel et al (2007) used a pharmaceutical definition (Edwards 2000) and applied it pragmatically to a prospective cohort study about adverse events in chiropractic. Serious adverse events were defined as: 'referred to hospital accident and emergency and/or severe onset or worsening of symptoms immediately after treatment and/or resulted in persistent or significant disability/incapacity'. Other graded definitions have been used such as: 'certain neurological deficits'; 'severe neurological deficits'; and 'serious complications' (Dvorak 1985). The problem with these definitions is that they do not cover the range of adverse events that may exist in manual therapies.

Manual therapy professions such as chiropractic, osteopathy and physiotherapy are obliged under

their codes of conduct to seek consent before administering treatment. Gaining *informed* consent, however, is difficult as we know little about risks involved with different treatments. As a first step towards quantifying risk, and providing patients with realistic estimates of the incidence of important therapy-related adverse effects, there is a need for a pragmatic definition of adverse events applicable to manual therapy. The aim of this study was, therefore, to seek an expert consensus definition of adverse events in relation to manual therapy by exploring understanding and meaning using a modified Delphi technique (Dalkey and Helmer 1963).

Method

Modified Delphi consensus study

A Delphi consensus study is a questionnaire survey of expert opinion conducted in 'rounds'; responses to each round of questionnaires are fed anonymously back to participants until an agreement or consensus is evolved or established. We selected this approach both to avoid key individuals' views dominating any open discussion and to ensure we could achieve international representation on our panel.

Developing the questionnaire

A focus group comprising a chiropractor, an osteopath, a GP, and a physiotherapist, all with specific and extensive interest and/or experience in the area of adverse events was convened. This group generated a taxonomy of adverse events and the initial content for the first round Delphi questionnaire. In addition, the results of the focus group were forwarded to a pharmaceutical industry specialist and an anaesthetist working in both primary and secondary care for their comments before the questionnaire was finalised.

Participants for Delphi study

To obtain a sample of experts we contacted: practitioners representing each statutory regulated manual therapy profession; health researchers with a research interest in this field; secondary care clinicians; pharmacists, general practitioners and researchers internationally. These were drawn from those who had published in this field, our own peer networks and practitioners attending the UK General Osteopathic Council 2008 conference. We then asked that any other interested parties (colleagues of those approached) be included, by free circulation of the questionnaire. We contacted all the identified experts in our panel via email and all subsequent participation in the study took place via email**.**

Questionnaires

The first consensus questionnaire sought opinion about constructs used to define 'major', 'moderate' and 'minor' adverse events. We made each construct into a bipolar statement and used a six point numerical rating scale to rank importance of each statement for 'minor', 'moderate' and 'major' adverse events. Example:

Distressing 1……2…….3……..4……5.....6 Not distressing

Participants were asked, systematically, to indicate on the numerical rating scale where a ‘major’, ‘moderate’ or ‘minor’ adverse event would lie using this continuum. We also sought comment on the hierarchical taxonomy decided by the focus group i.e. ‘major’, ‘moderate’ and ‘minor’.

For the second round of the Delphi study we presented the results back to the group (the numerical rating scale rankings) and asked members to further define those areas where there had been insufficient consensus in round one. We deemed 75% agreement as reaching a consensus. We also asked the group to classify a list of 36 potential adverse events (signs or symptoms) into ‘major’, ‘moderate’, ‘minor’ and ‘not adverse’. This list was developed by reviewing the adverse event literature and extracting adverse events recorded in articles. We used the constructs that had achieved consensus in the previous round, to provide a description/definition for ‘major’,’ moderate’ and ‘minor’ adverse events.
The questionnaire used in round three was designed to seek further consensus and opinion about adverse events; it depended on the outcomes from rounds one and two. Additionally, each of the questionnaires provided participants the opportunity for free text feedback about issues surrounding adverse events and the questionnaire.

Analysis
We used percentage agreement to determine the level of consensus in each round. Any responses to the free questions were coded into themes and summarised.

Results

Focus Group

The focus group discussed the issues surrounding adverse events in manual therapy and highlighted the need for a hierarchy that could: a) classify adverse events in order of importance and b) take into account 'non-adverse' adverse events. The group decided on a hierarchical taxonomy using the terms 'minor', 'moderate' 'major' and 'not adverse'. The definitions of these terms were to be decided by the Delphi process. The focus group generated constructs that they believed to be important descriptors providing meaning for adverse events. These constructs were made into bi-polar statements; the focus group proposed that the Delphi participants rank their beliefs about the importance, or not, of each level of adverse event according to each statement. The bipolar statements are shown in the first (least) and last columns (most) of Table 1.

Participants

The professions of the people chosen to be in our expert panel are shown in Table 2; response rates are given by profession as the percent of those participating at each stage of the consensus process. There were no responses from secondary care physicians (an orthopaedic surgeon, a vascular surgeon, a rheumatologist and an anaesthetist had been invited to participate) despite numerous follow-up emails.

Round one

We contacted 50 experts and practitioners: 25 (50%) of these responded. More than 74% of responders in round one agreed that the following were descriptors of 'minor' adverse events (ranked 1 or 2): mild, non-serious, function remains intact, transient/reversible, short term, no treatment alterations required, short term consequences and contained. More than 74% agreed that constructs/descriptors for 'major' adverse events (ranked 5 or 6) were: severe, unacceptable, requiring further treatment, serious and distressing. Overall there was little consensus achieved for descriptors of 'moderate' adverse events. 'Moderate' adverse events, ranked as 3 or 4, that achieved consensus, were described as being between mild and serious and could occur either during or after treatment (Table 1).

Round two

In round two we asked the Delphi panel to classify a list of 36 potential adverse events (signs and symptoms) as either 'major', 'moderate', 'minor' or 'not adverse' adverse events. The consensus-

agreed constructs from round one were used as definitions for ‘major’ and ‘minor’ adverse events to guide responders about their choice (Table 3).

The panel agreed (i.e. >74% of them) that ‘major’ adverse events were: coma, dislocation, fracture and loss of bladder and bowel control. For the rest of the signs and symptoms there was poor consensus (i.e. <75% agreement about whether the sign or symptom was either ‘major’, ‘moderate’, ‘minor’ or ‘not adverse’.
When we reviewed the data, the responses for ‘major’ and ‘moderate’ classifications were closely allied in distribution, as were ‘minor’ and ‘not adverse’ adverse events. For this reason we collapsed the classification of specific adverse events into ‘major/moderate’ and ‘minor/not adverse’ (Table 3).

The free response feedback question in round two indicated that the experts found the task of classifying specific potential adverse events very difficult without having any context or history about the event itself. The details requested/required by the experts concerned severity and duration.

Round three
In round three we explored severity and duration as these were seen as an important when classifying signs and symptoms as adverse events. We asked our panel to choose where each type of adverse event would lie in a matrix using severity and duration; their responses are shown in Table 4.

Definition of an adverse event

Our original intention of obtaining a short, succinct definition of an adverse event was not achieved. Instead, we have a layered pragmatic definition which is summarised in tabular form (Table 5). It shows:

- ‘Major’ adverse events are seen as medium to long term, moderate to severe and unacceptable;
  they normally require further treatment and are serious and distressing.
- ‘Moderate’ adverse events are described as the same as ‘major’ adverse events but only moderate in severity.
- ‘Mild’ and ‘not adverse’ adverse events are short term and mild, they are non-serious, the patient’s function remains intact, they are transient/reversible and no treatment alterations are required because the consequences are short term and contained.

Discussion

We believe that this Delphi study is the first of its type to address the issue of defining an adverse event in the context of manual therapy in a systematic, non individual and interdisciplinary way. We developed a layered approach to defining adverse events. The first layer identifies duration and severity and the second layer provides context and description about the nature of the adverse event; this enables us to classify any adverse event into a hierarchy of minor, moderate, or major.

This layered, pragmatic definition does not incorporate any underlying assumptions about causality, and therefore this is not an aspect of our definition. Whilst we recognise that causality is a huge area of concern it would detract from the usefulness of the definition in manual therapy as causality is often very hard to prove: by incorporating an element of causality into the definition it is unlikely to encourage practitioners to study, recognise and record adverse events. At present, the manual therapy professions are still trying to understand, quantify and identify risk associated with treatment and practitioners (Kerry 2008); a definition independent of causality may be more relevant for this purpose. No doubt as the manual therapy professions progress with research on this topic it will be possible to make a clear distinction between an adverse event (as discussed here) and an adverse treatment effect (any unfavourable or unintended response to treatment) as has been achieved in other fields of healthcare research (BSI British Standard (2003)).

This study has shown that using the term ‘adverse event’ tells us very little about the event that has occurred. Accounts of randomised controlled trials often state ‘no adverse events were reported’ or ‘‘n’ number of adverse events were recorded’ (Gross 2002) but this information is relatively meaningless unless the term ‘adverse event’ is elaborated upon. Our results show we can distinguish between ‘minor’ and ‘major’ adverse events. If outcome data for both trials and cohort studies included details about adverse events such as severity, duration and nature, we could start to understand and measure the prevalence and incidence of the different types of adverse events and whether they are ‘major’, ‘moderate’ or ‘minor’. Applying our definitions to such data may provide some useful distinctions as the repercussions that may occur for ‘minor’ as opposed to ‘major’ adverse events are different.

Most manual therapy trials and cohort studies report worsening or improvement of pain, function or mobility as outcome measures. Minimally clinically important changes can determine improvement and/or efficacy or worsening and/or harm. Worsening or deterioration after treatment may or may not necessarily constitute an adverse event; without detail about duration and severity we cannot

say if a negative or worsening reaction is a normal ‘within treatment’ variation or indeed an adverse event. Using our definition of adverse events and providing more information about ‘quality’ and ‘nature’ of any worsening of symptoms could enable researchers to achieve better classification and understanding of changes occurring in patients and the impact of any interventions being tested. Defining and recording adverse events in trials and cohort studies would enable researchers to study the incidence and prevalence of adverse events that occur in controlled study environments, as proposed by the CONSORT guidelines for reporting trial data (Ionnadis 2004).

There are a number of limitations to this study and indeed to the Delphi approach (Jones and Hunter 2000). Participants in Delphi studies are selected because they are experts in the field being researched but they may not necessarily be representative of the population to which findings are being targeted. Our expert panel included a range of professional disciplines, with both practising and non-practising clinicians, so we hoped to reduce this potential conflict. Our results did not show any major differences in classification between professions. We speculate that the most likely differences in responses would have been from secondary care consultants, but as none responded despite follow up their views are not represented in our study.

Our proposed definition and taxonomy will require further discussion and research, ideally it should be tested for reliability (inter, intra and test/re-test reliability) and validity to ensure its appropriate application.

Conclusions

The definitions obtained following this Delphi study can be used to categorise or classify adverse events in the context of manual therapy. Not only is a logical hierarchy presented, but also this definition allows for classifying those events that occur that may be regarded as ‘not adverse’.

References

BSI British Standards (2003): "BS EN ISO 14155-1:2003 - Clinical investigation of medical devices for human subjects – Part 1: General requirements", ISBN: 0 580 41393 4.

Dalkey N, Helmer O. An experimental application of the Delphi method for the use of experts. Management Science. 1963; 9 (3): 458-467

Dittrich R, Rohsbach D, Heidreder A, Heuschmann P, Nassenstein I, Bachman R, Ringelstein E, Jones J and Hunter D in Pope C and Mays N (Ed) Qualitative Research in Health Care (2nd Edition). BMJ Publishing, London. 2000 Chapter 5: 40:49

Kuhlenbaumer G, Nabavi D. Mild mechanical traumas are possible risk factors for cervical artery dissection. Cerebrovascular Disease. 2007; 23 (4): 275-81

Dvorak J, Orelli F v. How dangerous is manipulation to the cervical spine? Manual Medicine. 1985; 2: 1-4

Edwards I, Aronson J. Adverse drug reactions : definitions, diagnosis and management Lancet 2000; 356:1255-59

Gross A, Hondras M, Goldsmith C, Haines T, Peloso P, Kennedy C, Hoving J. Manual therapy for mechanical neck disorders: a systematic review. Manual Therapy. 2002; 7(73): 131-149

Ioannidis J, Evans S, Gottzsche P, O'Neill R, Altman D, Schulz K, Moher D for the CONSORT group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004; 141: 781-788

Kerry R, Taylor A, Mitchell J, McCarthy C. Cervical arterial dysfunction and manual therapy: a critical literature review to inform professional practice. Manual Therapy. 2008; 1-11

Leape L, Abbokire S. and WHO representatives. WHO draft guidelines for adverse events reporting and learning systems. WHO Press. Geneva Switzerland. 2003

Malone D, Baldwin N, Tomecek F, Boxell C, Gaede S, Covington C, Kugler K. Complications of cervical spine manipulation therapy: 5 year retrospective study in a single group practice. Neurology focus. 2002; 13 (6):

Stevinson C, Ernst E. Risks associated with spinal manipulation. Am J Med. 2002; 112:566 – 570

Thiel H, Bolton J, Docherty S, Portlock J. Safety of chiropractic manipulation of the cervical spine: a prospective national survey. Spine 2007; 32 (21): 2375-2378

Web references

WHO Collaborating Centre for International Drug Monitoring. The WHO Adverse Reaction Terminology - WHO-ART. Dec 2005. http://www.umc-products.com/graphics/3149.pdf (accessed 29.10.08)

Table 1. Round one: % agreement for each scale, 'major', 'moderate' and 'minor' adverse events

	Responses to 6 point numerical rating scale for:									
	Major adverse events			**Moderate adverse events**			**Minor adverse events**			
Construct (1 or 2)	1-2	3-4	5-6	1-2	3-4	5-6	1-2	3-4	5-6	**Construct (5 or 6)**
Mild	0	0	**76**	5	**91**	24	**95**	9	0	Severe
Acceptable	0	0	73	9	62	23	**91**	38	4	Unacceptable
Expected	0	5	43	5	50	48	**95**	45	9	Unexpected
Requires no further intervention	0	0	70	14	62	30	**86**	38	0	Requires further intervention
Non serious	0	15	**95**	5	65	5	**95**	20	0	Serious
Function remains intact	0	19	**85**	32	66	15	68	14	0	Function impaired
Transient/ reversible	5	41	**100**	36	55	0	59	5	0	Permanent
Not distressing	0	0	68	5	57	32	**95**	43	0	Distressing
Short term	5	25	**95**	36	70	5	59	5	0	Long term
No treatment alterations required	5	24	**81**	32	48	14	64	29	5	Treatment alterations required
Short term consequences	5	38	**100**	36	62	0	59	0	0	Long term consequences
Contained	10	37	**90**	55	63	10	35	0	0	Uncontained
Occurs after consultation	11	22	52	74	**78**	48	16	0	0	Occurs during consultation

Numbers in **Bold**= consensus >74%

Table 2. Delphi survey rounds: response rates by profession

Expert panel (n=50)*	**Round one (n/50)**	**Round two (n/50)**	**Round three (n/31)**
Chiropractors (n=3, 6%)	2 (4%)	3 (6%)	2 (6%)
General Practitioners (n=7, 14%)	4 (8%)	6 (12%)	3 (10%)
Osteopaths (n=12, 24%)	9 (18%)	11 (22%)	8 (26%)
Pharmacists (n=4, 8%)	1 (2%)	1 (2%)	1 (3%)
Physiotherapists (n=7, 14%)	2 (4%)	2 (4%)	0 (0%)
Psychologists (n=5, 10%)	1 (2%)	2 (4%)	1 (3%)
Researchers (n=8, 16%)	6 (12%)	6 (12%)	2 (6%)
Secondary Care consultants (n=4, 8%)	0 (0%)	0 (0%)	0 (0%)
Totals (50)	25 (50%)	31 (62%)	17 (55%)

* some people had dual roles, overseas representation = 7.

Table 3. Round two: classification of signs and symptoms

Consensus 75– 100%*	
'Major or moderate' adverse events	**'Minor or not adverse' adverse events**
Black out	Headache
Breathing difficulties	Muscle tenderness
Coma	Short term stiffness
Dislocation	Short term soreness
Fracture	Short term increase in pain
Loss or reduced bladder/bowel control	
Medium/long term loss of movement	
Medium/long term increased pain	
Stroke	
Transient ischaemic attack	
Visual disturbance	

*Signs and symptoms not achieving consensus: reduced range of movement, short term loss of movement, pins and needles, numbness, fainting, psychological distress, anxiety, panic attack, dizziness, muscle ache, increased pain on movement, palpitations, skin rash, depression, migraine, altered sensation, joint pain, radiating pain.

Table 4. Round three: severity and duration of 'minor', 'moderate', 'major' and 'not adverse' adverse events

>74% consensus	**Mild severity**	**Moderate severity**	**Major severity**
Short term duration (hours)	Minor Not adverse		
Medium term (days)		Moderate	Major
Long term (weeks)	Moderate	Major	Major

Table 5. Summary table of results: final definition of adverse events in manual therapy

Adverse Event	Duration	Severity	Descriptor
Major	Medium/long term	Moderate/severe	Unacceptable Requires further treatment Serious Distressing
Moderate	Medium/long term	Moderate	
Minor	Short term	Mild	Non-serious Function remains intact, Transient/reversible No treatment alterations required Short term consequences Contained
Not adverse	Short term	Mild	

Appendix B. Main table of articles

Author	Classification	Aim	Method	Evidence, quality	Pop Country	Sample size	Results of interest	Summary conclusion
Abbot N. et a. (1998)	N&T	Identify AEs in complementary and alternative medicine	Que'aire survey	IV Med	UK General public and GPs	686/1521 GPs responded	78 GPs (11%) reported 96 serious AEs after CAM treatment. 6 as a result of SM	CAM therapies like other health care interventions cannot assume to be risk free
Adams G. et al. (1998)	Prev Inc N&T	Ascertain reported frequency and severity of manipulation complications	Retrospective que'aire postal survey	IV Med	UK Physiotherapists	300 surveyed, adjusted response 48%, 143 manip. physios.	46 post SM complications reported by 19% of manipulators in 21 patients. Of these 65% lasted for <1 wk, 35% lasted>1 wk. No data about number of patients reported on	SM reported as relatively safe and widely used.
Anderson-Peacock E.et al. (2005)	Risk	To provide evidence about chiropractic manipulation for acute or chronic neck pain	Systematic review	I High	Databases search	Articles: Treatment 182 AEs 230 Risk 79 Update 121	AEs not addressed in most studies. When reported majority were minor	Recommend heightened vigilance for: any treatments to the neck, minimum rotation and upper cervical SM
Assendelft W. J. et al. (1996)	Prev Risk N&T	Review literature about risk and complications of SM therapy	Literature review	V Low	Case reports, retrospective surveys and review articles about complications post SM	295 case reports: VBA 165 cerebral complications 13, disc herniation and cauda equine 61, & other 56. 3 surveys.	VBA outcomes of 165 cases: 29 Deaths, 86 residual handicap, completed recovery 44, unknown 6. No new incidence or risk data	Difficult to estimate incidence. Possible under-reporting. VBAs difficult to prevent and treat. Avoid rotation SM. Risk information should be given to patients
Barrett A.J. & Breen A.C. (2000)	Prev Inc	Assess AEs first 48 hours post treatment	Prospective cross sectional que'aire postal survey of patients	II High	UK 9 chiropractic practices each recruiting 12 consecutive new adult patients.	80/108 que'aires returned (74%). 68 complete data sets	53% (36) reported AEs. No serious AEs reported. 78% of all AEs resolved by 48 hrs	High number of AEs reported most minor and transient
Boyle E. et al. (2008)	Inc	Determine whether VBAs incidence rates parallel chiropractic utilisation rates	Pop. based retrospective case note data	III High	2 Canadian provinces. Free chiropractic care clinics	Hospital diagnoses of VBA strokes (900 over 9 yrs). Billing data from Health Insurance plans(range 683 -734 pts pa per chiropractor) (13 million pop.)	VBA rate 0.750 - 0.855 per 100,000 person years, not associated with chiropractor utilisation. Incidence rate higher for men and those >45 years	VBA stroke rate does not seem associated with increased chiropractic utilisation rate

Bronfort G. et al. (2001)	Prev	Assess efficacy of SM for chronic headache	Systematic review	I Med	Database searches to 1998	9 trials reviewed reporting data on 683 participants	From pooled data. 5% withdrew due to complications and AEs after SM. 0 VBAs in any study reported	Recommends further rigorous research and follow up
Cagnie B. et al. (2004)	PrevRisk N&T	Identify risk factors for side effects associated with SM	Prospective observational que'aire survey	II High	Belgium Physios chiropractors and osteopaths and new patients	465 linked que'aires 930 SM recorded.	61% had a reaction of these 63% had 2 or more side effects. Associated risks: smoking, female, migraine. Predictor of side effects: smoking gender, age, medication use and region of manip.	Frequent common reaction to treatment for minor AEs which are benign and short lived. On average 2 manipulations per treatment
Carey P. F. (1993)	Inc N&T	To assess incidence of SM	Review of legal/insurance claims	IV Low	Canada legal/ins claims	13 CVAs. 100,000,000 SMs done by chiropractor over 5 yrs in 6 provinces and 50,000,000 Cervical SMs	Incident rate, 1: 3,846,153 cervical SM 0 deaths in the 5 yrs	Actual incidence unknown. Benefits out way risks
Cashley M. et al. (2008)	Risk Inc	Calculate rates of stroke risk in chiropractic population	Cohort comparison study	III High	UK chiropractors and Scottish borders study about stroke rates	Calculated estimate of patients receiving chiro SMs each year using 4 chiro clinics and 728 consecutive patients	Estimated chance per year of a chiropractor patient having a stroke within one day of a cervical SMs is 1.5% regardless of treatment	High background incidence of stroke and number of SMs performed annually, unsurprising that stroke patients may have recent history of SM
Cassidy M et al. (2008).	Risk	Investigate association between chiropractic care and VBA stroke	Population based case control and case cross over study	III High	Canada VBA stroke patients between 1993-2002, matched controls.	818 VBAs, 4 matched controls 3164. Health billing records for chiro and Primary Care Physician use	More VBA s associated with visits to PCPs than Chiros. 818 VBAs in 109,020,875 person years. Risk of VBA <45yrs OR 3.6 (CI 1.39-9.35) if seen Chiropractor in 30 days	VBA is a rare event. Increased risk of VBA with chiropractor and PCP visit, to seek help for headache and neck pain
Coulter I. (1998)	Inc Risk	To assess the appropriateness of SM	Consensus study and systematic review	I Low	Databases to 1998	25 controlled trials of low back pain 67 studies for cervical SM	Low back pain, 1500 pooled participants, 0 complications reported. 110 cases of complications from SM. Estimate 6.39 serious complications:10 million cervical SM and 1: 100 million lumbar SM	Risk of serious complications are very low and compares favourably to other therapies for same conditions
Dabbs V. & Lauretti W.J. (1995)	Inc Risk	To review literature to assess risk of death from stroke after SM	Literature review	V Low	Databases to 1998	Method not clearly stated	Some insurance data presented. Estimate rate of <1 stroke per 2 million cervical SM. 1 serious incident in 100,000cervical SM. Risk of death 1 per 400,000 patients treated	NSAIDs more risk to patient than SM
di Fabio R. (1999)	N&T	Review case reports to assess risk and benefit of SM	Literature review	V Low	Databases Articles between 1925 - 1997	177 case reports of complications post SM	20% arterial dissection. 18% deaths. 70% complications attributed to chiropractors, rest other manual therapists.	Until more is known about effectiveness and risk of cervical SM non thrust mobilization techniques should be considered

								as an alternative
Dittrich D.et al.(2007)	Risk	Investigate association between CAD and trivial mechanical traumas inc. SM	Case control study	IV High	Germany University hospital. 94 patients, 47 with CAD and 47 matched non CAD stroke patients	Interview/Que'aires to all CADs <60 years. Consecutive patients with stroke of a different etiology chosen as controls. MRI used to diagnose	No statistically sig difference with cervical SM and CAD. Recent infection in previous 7 days sig. OR 3.5	Cervical SM not a sig. risk factor, but mild mechanical traumas if grouped together.
Dupeyron A. et al. (2003)	Inc Risk N&T	Estimate frequency of strokes, myelopathies radiculopathy, VA accidents with SM	Que'aire survey of clinicians seeing arterial complications	IV High	NE France 240 surveyed, 133 responded reported 93 complications	Of the 93 complications 50% had a SM described as the origin of the complication, conducted within 24 hours of the complication	2-6 VBAs per 100,000 manipulations	SM should remain under strict medical control
Dvorak J& Orelli F. (1985)	Inc N&T	Explore the risks with manual medicine techniques	Que'aire survey of Swiss Soc of Man Med.	IV Med	Switzerland Manual medicine therapists	367 members surveyed about daily amount of SM. 55% (203) response	Cervical complication rate, 1:41,500 SM, severe complications 1:383,750 SM. Dizziness most common AE	Need for prospective studies to assess risk
Dvorak J. et al. (1993)	Inc N&T	To explore the frequency of complications of SM	Que'aire survey of Swiss Soc of Man Med.	IV Med	Switzerland Manual medicine therapists	425 members responded	Transient complications from cervical SM1: 16,716. Each physician will encounter 1 complication due to cervical SM in 38 years of practice.	Need for prospective studies to assess risk
Dziewas R. et al.(2003)	N&T Risk	Describe difference in the clinical course of VAD and CAD, define circumstances around them to determine predictors of poor outcome	Retrospective case history study	IV Med	Germany, university hospital neurology dept. All patients interviewed and followed up 6 months later	Retrospectively reviewed 126 consecutive patients with CAD and VAD from 1992 to 2001.	20/126 had previous SM (16%) and VAD or CAD. SM more likely to have VAD than CAD. At follow up 88 excellent recovery, 22 mild to mod health, 16 severe handicap or death	Neck pain associated more with VAD than CAD, headaches in half the sample. Risk factors smoking and hypercholesterolemia, VAD 30% more likely than CAD 6% in those who had a SM (20 patients)
Egizii G. et al. (2005)	Prev N&T	To determine use of SM by French doctors with a manipulation diploma	Que'aire survey, self report	IV High	French manipulation doctors who received a diploma between 1985 and 2002	140/234 doctors, (60%) anonymous responses	15 different techniques used. 26/140 declared to have caused a accident/incident with a SM in the course of their careers. 26 AEs post SM, 19 lasted less than 24 hours and 9 > 24 hours so minor	AEs raged from fractures, to reversible changes in motor function. No time scale reported as some clinicians in practice over 13 years others less. Incidence and prevalence indeterminable

Ernst E. (2001)	Inc	To summarise data from prospective investigations of SM AEs	Systematic review	I Med	Electronic databases plus peer and own	5 studies met criteria up to 1998	Major adverse events not common but minor AEs 50% after treatments	Transient events are frequent, serious probably rare but these are all based on estimates. More prospective studies needed
Ernst E. (2007)	N&T	Identify AEs of SM since 2001 -2007	Systematic review	I High	6 electronic databases between 2001 and 2006	28 articles, 32 case reports. 64 retrospective case series, 2 prospective case series, 4 case control studies, 3 surveys	Most common serious AE reported was VADs. Mild AEs occur in 30% - 61% of patients post SM	SM frequently associated with AEs but incidence data unknown. Reconsider policy towards use of SM in interest of patient safety
Garner M.J. (2007)	Prev Inc	Investigate the effectiveness of chiropractic care in Ottawa	Observational prospective cohort study	II Med	Canadian community pop. from chiro clinics over 17 months	366 patients presented and consented, 259 (80%) followed to discharge 196 followed up.	Mean 7.6 treatments over 12 week period. No AEs reported	Socioeconomic barriers exist for access to chiropractic care, further research necessary
Gross A. et al. (2007)	Prev Risk	Determine prevalence of risk factors associated with VAD after C trauma and SM	Literature review	V	Normal databases.	179 articles yielding 533 cases. 367 met final criteria for inclusion	Of the 367 VAD/Occlusion case studies, 160 (43%) were spontaneous, 115 (31%) assoc with SM, 58 (16%) with trivial trauma and 37 (10%) with major trauma	Data poor in literature so cannot answer research question
Haldeman S.et al. (1999)	N&T	Assess literature about neck movement and VAD and VBA	Literature review	V High	Databases to 1993	367 case reports.	160 spontaneous onset VADs, 115 after SM, 58 trivial trauma, 38 major trauma (3 both)	Data in the literature too poor to identify associations.
Haldeman S.et al. (2002) (a)	N&T Risk	Review patient risk and SM type to result in complications	Retrospective review of case studies	V Med	USA and Canada 64 cases post cervical SM complications	Malpractice case files of cerebrovascular insult over 16 years	92% history of sudden onset of new and unusual headaches and neck pain often associated with other neuro symptoms. No dose response relationship.	Stroke and VBD should be considered a random and unpredictable complication of any neck movement including cervical SM
Haldeman S. et al. (2002) (b)	Inc Risk N&T	Review accuracy of previous studies for risk factors assoc with complications	Review of case study cohort	V Med	USA and Canada 16 year period of legal cases	same cohort as study above	Screening showed no adverse responses (27/64 cases), 62/64 neuro. response, 40 immediate, 60 within 48 hours. Smoking, hyper tension and anticoag. therapy also associated	CVA after SM unpredictable and are a rare complication of SM
Haldeman S.et al. (2002) (c)	Inc	Assess the effect of referral bias on perception of SM	Data from insurer and a que'aire survey	IV High	Canadian chiropractors and general population	Qu'aire sent to 455 licensed chiros. 78% response rate(354). 43 cases identified in the study period (10 yrs).	23 cases p.a. of strokes post chiro SM Risk of stroke after chiro treatment 1: 8,063,974 or 1:5,846,381 after cervical SM.1: 1,430 practice years. Taking 30 years as a practice period 1: 48 chiropractors would see a stroke	Stroke patients see on average 9.5 clinicians post stroke

Hancock M.J. et al. (2007)	Prev	Investigation of NSAIDS or SM or both results in faster recovery	RCT	II High	Australia community GP sample	240 patients, 60 in each arm.	Extrapolate data, from SM and treatments, 120 had SM, max 12 treatments over 4 weeks, median 2.3 per week. So 120x4wks=480wksx2.3treatments= 1104 SM/treats and no AEs	Recovery equal with first line care, reported that no AE s were associated with SM therapy
Haneline M. T. et al. (2003)	Inc Risk	To determine relationship between Chiropractic and CAD	Lit review of case studies	V Med	Databases 1966-2000	13 Internal carotid artery dissections published.	Estimate > 7000 cases of ICAD per annum in the USA. Primary presentation neck pain and headache so likely to see a chiropractor not necessarily causal	No clear causal relationship between SM and ICAD and cases are scarce
Haneline M. T.et al. (2005)	Risk	Review of etiology of CAD	Literature review	V Low	1014 citations 20 relevant between 1994-2003	606 CAD cases, 321 CAD, 178 VAD	Of 606 CAD 371(61%) spontaneous, 178(29%) trivial or other trauma, 53(9%) SM	Risk of spontaneous dissection higher than SM and dissection
Hufnagel A. et al. (1999)	Risk N&T	Evaluation of risk factors with SM	Longitudinal case study	IV Low	Germany. Population advert.	10 people with stroke secondary to VAD post SM.	All patients uneventful history	Patients at risk of stroke after SM may not be identifiable a priori
Hurwitz E. et al. (1996)	Inc Prev N&T	Assess evidence for efficacy and complications of cervical SM	Systematic review	I High	4 databases	67 studies, 14 RCTs, 2 cohort studies, 14 case series, 37 case reports	Complication rate 5-10: 10 million cervical SMs	Complication rate small but potential needs consideration because of severe potential consequences
Hurwitz E. et al. (2004)	PrevR CT. Risk N&T	Compare effects of SM on AEs and to estimate effects of AEs	RCT	II High	USA Cervical SM vs cervical mobilization. Improvement and satisfaction measured at 4 weeks	960 eligible, 336 enrolled, 280 responded to qu'aires.	30% at least 1 AE. 1.44 OR of AE in SM arm. 85 patients reported 212 AEs. 120 in SM group and 92 in mob group. AEs varied from increased soreness or stiffness to weakness radiating pain and P&Ns.	AEs more likely with SM than mobilisation. AEs affect satisfaction ratings
Hurwitz E.et al. (2005)	Prev N&T	Assess frequency and predictors of AEs after chiropractic care for neck pain	RCT	II High	Same as above	336 participants 280 responded	Mod/severe neck disability at baseline strongly associated with adverse neuro symptoms OR 5.7(sig)	AEs common and more so with SM than mobilization. Consider conservative approach since little evidence of effectiveness of SM over mobilisation
Klougart N. et al. (1996) Part I	Inc Risk N&T	Estimation of irreversible CVAs after chiro treatment of cervical spine	Retrospective and non Retrospective survey	IV Med	Denmark Chiro. Assoc members 1978-1988 and patients on one day in1988	Chiros response rate 54% (125) 29,580 pts (response rate 72.5%)	1 CVA: 1.3mill cervical treatments 1:CVA :0.9mill upper cervical treatments Rotation thrusts high frequency	Incidence of CVA after chiro SMT low/advocates caution in use of rotational techniques 1st choice

Klougart N. et al. (1996) Part II	Inc Risk N&T	Estimation of reversible CVIs after chiro treatment of cervical spine	Retrospective and non Retrospective survey	IV Med	Denmark Chiro Assoc members 1978-1988 and patients on one day in1988	Chiropractor response rate 54% (125) 29,580 pts (response rate 72.5%)	1 CVI:120k treatments sessions. SM of upper c spine 4 X more assoc with CVI than lower c spine. Rotation thrusts high frequency	Treatment to lower cervical spine implicated in AEs as well as SM to upper cervicals
Leboeuf-Yde C. et al. (1997)	Prev Risk N&T	To investigate if work of Klougart in Denmark was applicable to Sweden ie was incidence of AEs to SM comparable	Prospective standardised que'aire survey	II Med	Swedish private chiro practices	Practice response rate 78%(66/86) 625 patients 1858 visits 73% target	Most common reaction was local discomfort in area of treatment (66%) Fatigue/Headache in 10% others 5% Reactions more common early in treatment series most reported by chronics and females	Largely confirm Klougart but no assoc with age Effects were physiological, common, benign, short lived
Lee K. P. et al. (1995)	Prev Inc N&T	To report neuro consequences of chiropractic adjustment evident 24 hr after treatment and deficits at 3mth follow up	Retrospective que'aire	IV Med	USA Members of American academy of Neurology. Jan 1990-Dec1991 Pts age 21-60yrs	486 surveyed 36% response (177)	126 (71%) reported zero neuro AEs. 51 (29%) reported 102 neuro AEs 30 cases or radiculopathy 73% in cervical	Insufficient data to determine frequency of chiropractic complications because small sample, ltd to California, low response rate
Malone D. G. et al. (2002)	Prev Inc Risk N&T	To report cases and extrapolate regional incidence rate from case series	Retrospective case series	IV Low	USA Single group neuro practice (6 surgeons) Oklahoma over 5yrs	1712 cases/172 Cervical SM	32 worsening symptoms. 21 irreversible complications 0 deaths Incidence, 1 irreversible complication:45,600 cervical SM	Cervical SM may worsen pre-existing disc herniation and myelopathy/radiculopthy in spondylosis. Cervical SM possibly associated with higher incident rates than thought
Margarey M.E. et al. (2004)	Prev Inc N&T	Assess the effectiveness of pre manipulative testing and the incidence of AEs from cervical SM	Que'aire survey	IV Med	Australia Physiotherapists	480/740 physios responded (65%)	AEs reported at 1: 1000 years of practice. Common effects potentially related to VBIs. 0 major complications reported	Risk of serious AEs low. Use of pre manipulative testing variable
Mascalchi M. et al. (1997)	Risk	To investigate mechanisms of pathophysiology of VAD	Retrospective case review	V Low	Italy Patients over 7years in 2 hospitals	4500 cervicocranial arteriograms	4 patients had history of trauma or SM. prior to VAD 10 pts had "spontaneous" VAD Incidence of VAD 14/4,500	MRI more useful than MRA for diagnosing VAD in acute phase. Low incidence of VAD
Michaeli A. (1993)	Prev Inc Risk N&T	Establish prevalence and nature of complications following SM	Retrospective self report Que'aire survey	IV Med	Australian registered physios	153/250 responded 61%. 67% 103 manipulated	29 patients had 52 complications. All recovered in, on average 6.2 days	Sm performed by physiotherapists in South Africa is relatively safe.

Oliphant D. (2004)	Inc Risk	To provide qualitative review of risk of SM in treatment of lumbar disc herniation and estimate risk of severe AE	Systematic review and risk assessment compared to NSAIDS and surgery	I Med	8 Reviews 9 prospective/ retrospective surveys 2 surveys	2100 patients, 13100 treatments in prospective/retrospect ive surveys	Risk estimate of SM worsening herniation and cauda equina in those with lumbar disc herniation <1:3.7mill	SM apparently safe therefore should stimulate increased use in conservative treatment of lumbar disc hernias
Oppenheim J. S et al. (2005)	Risk N&T	To identify risk factors in SM and clarify non vascular complications	Record review	IV High	USA Patients from a neurosurgical practice between1995-	18 patients with worsening of symptoms during SM treatment	Injuries sustained to cervical, thoracic, lumbar spine resulted in myelopathy, radiculopathy, cauda equina, paraparesis. 89% required surgery	SM assoc with signif. Complications. Non vascular complications may be under reported because of strict temporal criteria .Current study may also under estimate risk
Rivett D&, Milburn P. (1997)	Prev Inc Risk N&T	To explore extent and range of serious AEs with SM	Que'aire survey	IV High	New Zealand Neurologists, neuro, orthopeadic, vascular surgeons	146/230 (63%) responded reporting complications following SM in previous 5 years	42 incidents reported, cervical SM accounted for 62%. 14 CVAs. Physios responsible for 1/3, chiropractors for more than half	Serious complications can arise from SM. Prospective studies needed to ascertain incidence
Reuter U.et al. (2006)	Risk N&T	To describe clinical characteristics of patients with cerebral ischaemia and VAD due to cervical chiro SM.	Retrospective clinical survey	IV Med	Germany Patients of University affiliated Neuro depts in over 3yrs	21/32 Dept participated11centres reported O pts with VAD related to chiro manip. 13 reported centres 36 pts with assoc symptoms	Symptoms started in 72% after 2 days. 5 showed clinical symptoms during treatments and 4 within one hour. In 20 pts prominent symptoms in brain areas supplied by VA	"Our data point to a yet to be precisely determined substantial risk including death for VA after neck chirotherapy"
Rothwell D.et al. (2001)	Inc Risk	Test association between chiro cervical SM and dissection/occlusion of VA	Nested case control study	III Med	Canada Hospital records in Ontario 1993-1998	582 cases age stratified ,<45 >45	In those ,<45 yrs VBA 5 times more likely than control within 1 wk of manipulation also 5 times more likely to have had 3 or more visits before VBA Only assoc between risk of VBA and manip. in<45 only	Analysis consistent with + assoc in young adults but not conclusive
Rubinstein S. M. et al. (2008)	Prev Risk N&T	Determination of prognostic variables for AEs in those with neck pain having chiro care.	Prospective multicentre cohort study	II High	Netherlands Pts in private chiro clinics in between Spt 2004 and April 2005	579 recruited 529 fulfilled inclusion criteria (10 consecutive treatments) 4,891 consultations	56% had AE after 3 treatments 14/15%=high intensity. Most common reported events= musculoskeletal or pain. Nonmuscular events=<8%	Of 60 independent variables only 4 predictive of AE after chiro treatment. 3 can be identified by practitioner (use of rotation, work status of pt, long prior duration of pain). Visit to GP prior to treatment is protective
Rubinstein S. M. et al.	Risk N&T	Describe clinical outcomes and AEs	Prospective multicentre	II High	Netherlands Patients treated	Same study as above	1% (5) subjects much worse at 12 months. 0 serious AEs reported	AEs are common but rarely severe. Most patient report long

(2007)		in patients treated for neck pain by chiropractors	observational cohort study		by members of Chiro Assoc			term recovery therefore benefits of chiro care for neck pain seem to outweigh risks
Rubinstein S.M. et al. (2005)	Risk	To review pathogenesis of CAD	Systematic Review	I High	Databases 1966-2005	31 case control studies examining 8 risk factors including trauma to neck (SM)	Association of trivial trauma ie neck manipulation OR 3.8 95% CI 1.3 to 11	Strong association for risk factors with a genetic component and trivial trauma(ie cervical SM) but studies contain bias common in case control studies
Senstad O. et al. (1996) (a)	Prev N&T Risk	To determine if side effects of SM can be predicted and if so are they patient or treatment related	Prospective clinic based survey	II High	Norway Pts treated by chiro clinics	102 chiros (response rate 70%)12 consecutive patients attending for up to 6 treatments (1058 pts and 4,712 treatments)	Results divided into "common" and "uncommon" side effects. Females report more side effects. Gender difference in type of reactions. More reactions in first treatment sessions, when more than one area treated and when T spine only treated. No predictors	Clinical significance of indentified predictors is unclear
Senstad O. et al. (1997)	Prev N&T Risk	To study type/frequency/characteristics of unpleasant side effects of SM	Prospective clinic based survey	II High	Norway Pts treated by chiro clinics	Same cohort as above	At least one reaction reported by 55% of patients over 6 treatments: local discomfort 53% headache12% tiredness 11% radiations 10% Reaction mild to moderate in 85%?64% appeared within 4 hours/ 74% gone within 24 hours 5%=uncommon reactions. No reports of serious	Study has confirmed previous pilot but has failed to identify empirically generated examples of side effects
Senstad O. et al. (1996) (b)	Prev Inc Risk N&T	Appraise types of AEs after SM	Prospective cohort study	II High	Norway 10 chiropractors, 10 consecutive patients 6 treatments max	95 patients 368 treatments in total.	AE reported 34% of treatments, 90% moderate or slight, 83% disappeared after 24 hours and all after 72 hours. No sever AEs reported	
Shekelle P. G. et al. (1992)	Risk N&T	Review use, complications and efficacy of SM for low back pain	Literature review	V Med	Databases 1952 – 1992	25 RCTs reviewed	Pooled subjects from RCTs = 1500 SM patients 0 AEs reported	Complication rates are unknown
Smith W. S.et al. (2003)	Risk	To determine if SMT is an independent risk factor for CAD	Nested case control design/retrospective case reviews	IV Med	USA 2 Academic stroke centres between 1995-2000 at	151 cases/ patients under 60 yrs with CAD, ischemic Stroke or TIA	Patients with VAD more likely to have had SM within 30days (14% vs 3%); have had head/neck pain preceding stroke/TIA (76%vs 40%) and to be current consumers of alcohol (76%vs 57%)	SM is independently associated with VAD even after controlling for neck pain. 6 of 7 dissections closely related to SM were of VA SM may aggravate pr-existing conditions

Terrett A. G. (1987)	Risk N&T	To review the incidence of and analyse 107 cases of vascular accidents following cervical SM	Retrospective case review	V Low	Identified cases between 1934-1984	107 cases, VBA strokes after SM	No sex/age correlation: increased level of accidents in 30/45 age range appears to be a reflection of increased usage in this group	Chiros can show treatment is safe and effective. (Conclusions not grounded in data)
Thiel H. W.et al. (2007)	Risk N&T	To estimate risk of serious and minor AE following cervical SM	Prospective national survey	II High	UK Members of British and Scottish Chiro Association patients	1,183 chiros (31.9% response 377)19,722 patients. 28, 807 treatments 50,276 cervical SMs	No reports of serious AEs Estimated risk of serious AE immed. post SM.1:10000 up to 7 days post treatment 2:10000:up to 7 days post treatment 6:10000 minor neuro side effects immed. post treatment. 16:1000 up to 7 days post treatment	Minor side effects relatively common. Risk of serious AEs up to 7 days post treatment low
Thiel H.W. et al.(2008)	Risk N&T	To identify predictors for improving or worsening with cervical SM	Prospective national survey	II High	UK Members of British and Scottish Chiro Association patients	As above same data set	Immediate worsening predictors: neck shoulder or arm pain, headache, numbness tingling in upper limbs, upper mid back pain, fainting dizziness light headedness. Presence of any 4 increased probability from 4.4 to 12%	Data not robust enough for a clear prediction rule for immediate worsening
Vohra et al. (2007)	Prev Risk N&T	Analyses data about AEs and peadiatric SM	Systematic review	I High	8 databases to 2004	13 studies, 2 RCTs, 11 observational studies	14 cases of direct AEs as a result of SM. 9 serious, 2 moderate, 3 minor. Plus 20 cases of indirect AEs	Serious AEs may be associated with peadiatric SM. Need for prospective studies

Appendix C. Quality review table

Author and title	Is aim stated clearly?	Is methodology appropriate to the aim?	Is sample pop. inclusion criteria clearly defined?	Was sample power adequate?	Intervention method clearly described?	Is professional status described?	Were dropouts followed up and reported?	Were outcome measures objective?	Were results clearly reported?	Are conclusions supported by the data?	Are AEs clearly described/ defined?	Is AE data collection tool described?	Was mode of collection described?	Was timing of data collection described?	Is temporality/causation considered?	Qual Rating
Abbott N. et al. (1998)	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Med
Adams G. et al. (1998)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Med
Anderson-Peacock E. et al. (2005)	Yes	Yes	Yes	No	Yes	Yes	N/A	N/A	No	Yes	Yes	N/A	N/A	N/A	N/A	High
Assendelft W.J.et al. (1996)	Yes	Yes	No	No	No	Yes	N/A	Yes	Yes	No	Yes	No	No	No	No	Low
Barrett A.J. & Breen A.C. (2000)	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Boyle E. et al. (2008)	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Bronfort G. et al. (2001)	Yes	Yes	Yes	Yes	Yes	No	N/A	Yes	Yes	N/A	No	No	N/A	N/A	No	Med
Cagnie B. et al. (2004)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Carey P.F. (1993)	Yes	No	No	N/A	No	Yes	N/A	No	Yes	Yes	Yes	No	No	No	Yes	Low
Cashley M. et al. et al (2008)	Yes	Yes	Yes	No	No	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Cassidy M. et al. et al. (2008).	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes	High
Coulter I. (1998)	No	N/A	Yes	N/A	No	N/A	N/A	No	No	No	No	No	No	No	No	Low
Dabbs V. & Lauretti W.J.	Yes	No	No	N/A	No	N/A	N/A	Yes	Yes	Yes	Yes	No	No	No	No	Low

(1995)																
di Fabio R. (1999)	Yes	No	No	N/A	No	Yes	N/A		Yes	Yes	Yes	Yes	Yes		Yes	Low
Dittrich R. et al. (2007)	Yes	Yes	Yes	N/A	Yes	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Dupeyron A. et al. (2003)	Yes	Yes	Yes	N/A	N/A	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	High
Dvorak J. & Orelli F.V.(1985)	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	No	No	No	No	Yes	Med
Dvorak J. et al (1993)	Yes	No	Yes	No	No	Yes	N/A	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Med
Dziewas R. et al. (2003)	Yes	No	Yes	N/A	No	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Med
Egizii G. et al. (2005)	Yes	Yes	Yes	N/A	Yes	Yes	?	Yes	Yes	N/A	Yes	Yes	Yes	Yes	?	High
Ernst E. (2001)	Yes	Yes	No	N/A	N/A	N/A	N/A	No	Yes	Yes	?	Yes	Yes	Yes	Yes	Med
Ernst E. (2007)	Yes	No	Yes	N/A	No	N/A	N/A	No	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Garner M.J. et al. (2007)	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	No	Med
Gross A.R. et al (2007)	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	High
Haldeman S. et al. (2002)	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Haldeman S. et al. (1999)	Yes	Yes	Yes	N/A	Yes	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Haldeman S. et al. (2002)	No	n/a	Yes	n/a	Yes	No	n/a	n/a	Yes	No	Yes	Yes	Yes	No	Yes	Med
Haldeman S. et al. (2002)	Yes	Yes	Yes	n/a	Yes	No	n/a	n/a	Yes	No	Yes	Yes	Yes	No	Yes	Med
Haneline M.T.et al. (2003)	Yes	No	No	N/A	No	No	N/A	No	Yes	Yes	No	N/A	N/A	N/A	Yes	Med
Haneline M.T.et al (2005)	Yes	No	Yes	N/A	No	No	N/A	No	Yes	Yes	No	N/A	N/A	N/A	Yes	Low
Hufnagel A. et al. (1999)	No	No	Yes	N/A	Yes	No	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	No	Low

Hurwitz E.L. (1996)	Yes	Yes	Yes	N/A	No	No	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	No	High
Hurwitz E. L. et al. (2004)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Hurwitz E.L. et al. (2005)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Klougart N. et al. (1996) (I)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	N/A	No	Med
Klougart N. et al. (1996) (II)	Yes	Yes	Yes	No	Yes	Yes	N/A	No	Yes	Yes	No	Yes	Yes	N/A	No	Med
Leboeuf-Yde C. et al. (1997)	Yes	Yes	Yes	N/A	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Med
Lee K.P. et al. (1995)	Yes	Yes	Yes	N/A	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	Med
Malone D.G. et al. (2002)	Yes	No	Yes	N/A	No	No	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	No	Low
Margarey M.E. et al. (2004)	Yes	Yes	Yes	N/A	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	N/A	No	Med
Mascalchi M. et al (1997)	No	No	Yes	N/A	No	No	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A	No	Low
Michaeli A. (1993)	Yes	Yes	Yes	N/A	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	N/A	No	Med
Oliphant D. (2004)	Yes	Yes	Yes	N/A	No	No	N/A	N/A	Yes	Yes	N/A	N/A	N/A	N/A	No	Med
Oppenheim J.S. et al. (2005)	Yes	Yes	Yes	N/A	Yes	No	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	Yes	High
Rivett D.A & Milburn P.(1997)	Yes	Yes	Yes	N/A	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	High
Reuter U et al.(2006)	Yes	Yes	Yes	N/A	No	No	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Med
Rothwell D.M. et al. (2001)	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Med
Rubinstein S.M. et al. (2008)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Rubinstein S.M. et al. (2007).	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

Senstad O. et al. (1996a)	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Senstad O.et al. (1997)	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Senstad O.et al. (1996 b)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	High
Shekelle P.G. et al. (1992)	Yes	Yes	Yes	N/A	Yes	No	N/A	No	Yes	Yes	No	N/A	N/A	N/A	No	Med
Smith W.S. et al. (2003)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Med
Terrett A.G. (1988)	Yes	No	No	N/A	No	No	N/A	Yes	Yes	Yes	No	No	No	N/A	No	Low
Thiel H.W. et al. (2007)	Yes	Yes	Yes	Yes	No	Yes	N/A	No	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Thiel H.W. et al. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Vohra S. et al (2007)	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

Appendix D. Table of RCTs

RCTs Author	Population	Cohort/ arms numbers	Manual therapy	AEs reported	Number of AEs
Bove G. et al.(1998)	Outpatients chiropractic NHS facility Denmark, 75 episodic tension type headache patients	Soft tissue and SM (37) vs soft tissue and placebo laser (control) (38)	8 treatments over 4 weeks deep friction massage and cervical SM as deemed appropriate (high velocity low amplitude).	No mention of how collected or how 'side effects' defined	0 in any group 0/37
Bronfort G.et al .(2001)	191 adults with chronic mechanical neck pain, recruited via newspaper adverts	SM and low technology exercise (63) vs MedX exercise (60) vs spinal manipulation (64)	20 x 1 hour visits over 11 weeks. Short SM to cervical and or thoracic spine with light soft tissue massage if necessary	Side effects data collected described as increases in neck or headache pain, increased radicular pain and severe thoracic pain	Increase in neck or headache pain. SMT/Ex 8, Med X 9 and SMT 6. Increased radicular pain SMT/Ex 1, severe thoracic pain SMT 1. 16/127
Burton A. et al. (2000)	Sciatic pain patients	SM (20) vs chemonucleolysis (20)(single injection of chymopapain)	Manipulation (15mins treatment over 12 weeks), soft tissue, stretching to lumbar and buttock musculature low amplitude passive articulation and judicious use of SM to one or more lumbar articulations	Major complications	0
Cherkin D. C.et al. (2001)	262 USA Adults with chronic low back pain in a primary care facility	acupuncture (94) vs massage (78) vs self care education (90)	Massage Swedish, deep tissue, neuromuscular trigger and pressure point and energy techniques administered as deemed fit.	No serious adverse events reported by any participants. But 13% in the massage group reported significant discomfort or pain during or shortly after treatment.	10 people of 78
Cleland et al. (2007)	Physical therapy patients in a USA rehabilitation clinic with neck pain	Nonthrust mobilisation/SM (30) vs thrust mobilisation/SM (30)	Non thrust mobilisation to thoracic spine and SM between T1 and 4	Side effects described as aggravated symptoms, neck stiffness, headache, radiating symptoms and muscle spasm	9/30 in non thrust group and 10/30 in the thrust group

Evans R. et al. (2003)	USA adults with acute and sub acute neck pain recruited via community targeted adverts	Chiropractic care (10) vs medical care (9) vs self care education (9)	chiropractic SM with light soft tissue if necessary	Reported side effect for each arm of trial: neck or low back pain, tingling in arm, neck stiffness muscle soreness, headache, dizziness, rash, heartburn, gastric distress drowsiness.	Self education 3/9, manipulation 9/10, medication 5/9
Ferreira M. L. et al. (2007)	Adults with non specific chronic low back pain from physical therapy departments in Australian teaching hospitals	General exercise (80) vs motor control exercise (80) vs SM (80)	Joint mobilisation and or SM applied to the spine or pelvis	" no adverse events were reported" (not defined)	0/80
Giles L.G. et al. (1999)	77 chronic spinal pain patients from a Specialist spinal outpatient hospital unit, Australia	Needle acupuncture (20) vs NSAID medication (21) vs chiropractic spinal manipulation (36)	High velocity low amplitude SM in 6 treatment over a 4-6 week period	Side effects only mentioned not defined. Mentions gastric symptoms for medication group	0/20 for acupuncture, 0/36 for SM and 3/21 for medication
Giles L & Muller R. (2003)	109 chronic spinal pain patients from a Specialist spinal outpatient hospital unit, Australia	needle acupuncture (34) vs NSAID medication (40) vs chiropractic spinal manipulation (35)	High velocity low amplitude SM in 6 treatments over a 4-6 week period	Side effects only mentioned not defined.	0/34 for acupuncture, 0/35 for SM and 7/40 for medication
Hancock M. et al. (2007)	Patients with low back pain of less than 6 weeks in 40 GP practices	SM + diclofenac (60) vs placebo SM diclofenac (60) vs SM and placebo diclofenac (59) vs Placebo SM and placebo diclofenac (60)	SM therapy (max 12 treatments over 4 weeks), HVT administered	Serious adverse reactions	0
Hawk C. et al. (2005)	111 adults with sub acute or chronic low back pain from a chiropractic research clinic USA	chiropractic SMand trigger point therapy (54) vs sham SM and effleurage (57)	Flexion distraction chiropractic SM and trigger point therapy to the lumbar spine and localised areas	Reported a non serious AE described as a worsening of back pain during the treatment visit, this patient was in the active SM group. One withdrew not related to AEs	1 out of 54
Hawk C.et al.(2006)	81 elderly chiropractic patients, USA	Chiropractic SM (41) vs non SM mindbody approach (40)	Soft tissue, heat, ultrasound, interferential current advise on exercise and or nutrition and SM	AE defined as any symptom that arose within 24 hours of the treatment session lasting over 24 hours from onset	0 AEs reported 0/41

Hay E. M.et al.(2005)	402 primary care physiotherapy back pain patients in the UK	Brief pain management programme (201) vs manual physiotherapy (201)	SM therapy techniques ie articulation -mobilisation and SM and soft tissue plus advice and exercise	1 AE recorded after the initial assessment that was reported to the data monitoring and ethics committee.	0/201
Hoeksma H. L. et al. (2004)	109 hip OA patients from hospital outpatients clinic in the Netherlands	Manual therapy (56) vs exercise therapy (53)	SM and mobilisation of hip joint twice weekly for 5 weeks. Traction and SM (high velocity thrust).	3 discontinued due to increase in complaint in manual therapy group and 2 in the exercise group.	0 other AEs reported 0/56
Hondras M. A. et al. (1999)	138 USA adult females with primary dysmenorrhea	SM therapy (69) vs low force mimic manoeuvre (69)	Chiropractic SM, side lying high velocity short lever low amplitude thrust from T10-L5 and sacro-iliac joints.	2 LFM women and 3 SM women reported one episode of soreness in low back for 24- 48 hours that was self limiting. 0 other AEs reported	2/69 and 3/69 and 0/138 major AE s reported in either group
Hoving J. L.et al. (2002 and 2006)	183 adult outpatients with nonspecific neck pain in Netherlands	Manual therapy (60) vs exercise therapy (59) vs GP care (64)	Passive movement , muscular mobilisation, articular mobilisation, low velocity. HVTs not included	Minor, benign, short term adverse reactions such as headache, pain, tingling, dizziness	Manual therapy - 42 reports from 60 people, physical therapy - 39 reports from 59 people, cont GP care - 22 reports from 64 people
Hsieh C. Y.et al. (2002)	200 people from the general public with subacute low back pain	Backschool programme (48) vs myofascial therapy programme (51) vs joint manipulation (49) vs combined joint manipulation and myofascial therapy (52)	Chiropractic high velocity, short amplitude manipulations inc drop table manipulations.	Transient exacerbations of symptoms except one case of constant tinnitus.	7/52 combined group, 6/49 joint manipulation, 4/51 myofascial group, 6/48 backschool group
Hurwitz E. L.et al. (2002, 2006)	90,000 to 110,000 members of a health care network in USA, outpatients with ambulatory low back pain	medical care only (170) vs medical care + physical therapy (170) vs chiropractic care only (169) vs chiropractic care and physical modalities (172)	Chiropractic only group had SM. Physical therapy involved heat, cold, ultrasound, EMS, exercise, soft tissue and joint mobilisation. Physical modalities as above but with no joint mob or soft tissue	" no known study related AE requiring institutional review board notification were experienced by patients in any group	0/169
Hurwitz E. L.et al. (2002, 2004 and 2005)	90,000 to 110,000 members of a health care network in USA, outpatients with ambulatory neck pain	Chiropractic SM (171) vs spinal mobilisation (165) SM with and without heat and with and without EMS vs	SM, high velocity, low amplitude thrust with minimal extension and rotation to 1 or more upper thoracic or cervical spine segments. Mobilisation group 1 or more low	No known study related AEs. But manipulation group more likely than others to experience transient minor discomfort	(27/171) vs (14/165) 85/280 participants reported adverse symptom(s) (30.4%). 48/171 SM group, 37/165

		mobilisation with and without heat and with and without EMS.	velocity, variable amplitude movements within patients passive range Other groups as above with heat or electrical stimulation.	during initial 4 week treatment. Experience of discomfort or unpleasant reaction from chiropractic care in the last 2 weeks. Rated from 1-10 for each symptom described, with a timescale for onset. Categories: increased neck pain/ stiffness/ soreness, radiating pain or discomfort, tiredness/fatigue, headache, neurological symptoms, other	Mobilisation group.
Jull G. et al. (2002)	Adults from GPs in Australia with cervicogenic headache.	SM (51) vs SM plus exercise (49) vs therapeutic exercise (52) vs control (48)	SM, low velocity cervical joint mobilisation and/or high velocity SM following normal clinical practice	" no important AEs were reported in this study" no definition of important given	0/51 manipulation only
Nelson C. F. et al. (1998)	Chiropractic outpatient clinic in Canada, patients with migraine headaches 218	SM (77) vs amitryptiline (70) vs combined (71)	High velocity low amplitude short lever arm to the cervical spine, massage and trigger point therapy	Side effects for SM group were benign, infrequent, mild and transitory that did not necessitate withdrawal	0/77. 10% of amitryptiline group had to withdraw due to side effects and 58% experienced medicine side effects
Plaugher G.et al.(2002)	23 adults with hypertension in a private practice chiropractic clinic USA	chiropractic adjustment (9) vs brief massage (8) vs control (6)	Spinal adjustment short lever arm specific contact manipulation	" No AEs or complications occurred in any of the study participants..."no subjects withdrew or were removed from the study because of an AE, nor did any subject report an AE"	0/17
Santilli V. et al. (2006)	102 ambulatory adults with sciatic pain with disc protrusion	SM (53) vs simulated SM (49)	Range of motion assessment, soft tissue and brisk rotational thrusting. Simulated technique did not include the thrusting	" No AE were reported"	0/53 and 0/49

Sawyer C. E. et al. (1999)	20 children (6 months - 6 years) with otitis media from general population adverts in USA	Chiropractic SM (9) vs sham SM (11)	Active - Upper cervical low amplitude high velocity manual SM. Sham - static and motion palpation and light touch but no thrust.	"No reports of serious side effects as a result of either active or placebo chiropractic treatments" In active group 1 sore 1 irritable after treatments resolved within a few days. 1 in sham group excessive crying after treatment	2/9 and 1/11
Schiller L. (2001)	30 adults with thoracic spine pain from general population in South Africa	Thoracic SM(15) vs non functional ultrasound (15)	Standard manual thrust chiropractic adjustment, high velocity low amplitude	Moderate local discomfort was a common complaint after first treatment and manipulation to the thoracic spine.	NO data given
Skargren E. I.et al. (1997 and 1998)	323 Patients with Back/neck problems in primary care in Sweden	Chiropractic (179) vs physiotherapeutic care (144)	80% had SM treatment all treatment was at the discretion of the clinician	"No complications due to treatment were reported from any therapist or patient"	0/179 and 0/144
Strunk R. G. & Hondras M. A. (2008)	USA adults with chronic and sub acute neck pain recruited via community targeted adverts	Cervical SM (3) vs combined SM and muscle energy technique (3)	High velocity low amplitude cervical SM Other group high velocity low amplitude thoracic SM with muscle energy technique	1 severe discomfort or unpleasant reaction and 1 Mild increased pain/stiffness and dizziness/ imbalance	2 / 6
Tuchin P. J. et al. (2000)	Chiropractic research centre patients in Australia	Cervical SM therapy (83) vs control (detuned interferential (40)	Chiropractic SM passive manual manoeuvre of short amplitude high velocity thrust	1 Person left the study due to soreness after SM and 1 left due to worsening migraine caused by chiropractic	2 /83
UK BEAM (2004)	Low back pain patients in UK	Usual/GP care (353) vs manipulation(310) vs exercise (338) vs manipulation and exercise (333)	Manipulation package	'Serious adverse events'	0 in any group
Vincenzo et al (2001)		Lateral glide mobilisation (8) vs placebo (8) vs control (8)			0 adverse events
Williams N. H.et al. (2003)	201 Primary care patients, Wales, with back or neck pain	Usual GP care (109) vs GP care and additional 3 sessions of Ost SM (92)	Manual therapy 3-4 sessions, intervals 1-2 wks SM and advice about keeping active avoiding bed rest	Definition of Ae not provided	0/92 of SM group in trial reported

36 studies reviewed
SM =spinal manipulation
AE = adverse event
OR = Odds ratio

Appendix E. Quality appraisal of RCTs

RCTs	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Total	Qual
Author	**2**	**5**	**4**	**3**	**4**	**12**	**10**	**5**	**5**	**5**	**5**	**5**	**10**	**10**	**5**	**5**	**5**	**100**	
Bove et al. (1998)	2	5	2	1	2	0	10	0	0	0	5	0	10	0	5	0	5	47	Lo
Brontfort et al (2001)	5	4	3	4	6	10	0	0	0	5	0	10	10	5	5	5	74	74	Med
Burton et al (2000)	2	5	2	0	0	0	10	5	0	0	5	0	10	10	5	0	5	59	Med
Cherkin et al. (2001)	2	5	2	0	4	6	10	0	0	0	5	0	10	0	5	0	5	54	Med
Cleland et al (2007)	2	5	4	3	4	0	10	0	0	0	5	0	10	0	5	5	0	53	Med
Evans et al (2003)	2	0	4	3	4	0	10	5	0	0	5	0	10	0	5	0	5	53	Med
Ferreira et al. (2007)	2	5	4	3	6	6	10	0	0	0	5	0	10	10	5	5	5	76	Hi
Giles et al. (1999)	2	5	4	0	0	0	10	0	0	0	5	0	10	10	5	0	0	51	Med
Giles, Muller (2003)	2	5	4	3	4	0	10	0	0	0	0	0	10		5	5	5	63	Med
Hancock et al (2007)	2	5	4	0	4	6	10	0	0	0	5	0	10	0	5	5	0	56	Med
Hawk et al. (2005)	2	5	2	3	4	2	10	0	0	5	5	5	10	10	5	5	5	78	Hi
Hawk et al. (2006)	2	5	2	3	2	0	10	0	5	0	5	0	10	10	5	5	5	69	Med
Hay et al. (2005)	2	5	4	0	0	12	10	5	0	0	5	0	10	0	5	5	5	68	Med
Hoeksma et al. (2004)	2	5	4	3	0	6	10	0	0	0	5	0	10	10	5	5	5	70	Med
Hondras et al. (1999)	2	5	4	3	2	6	10	0	0	5	5	0	10	10	5	5	0	72	Med
Hoving et al. (2002, 2006)	2	5	4	3	4	6	10	5	5	0	5	0	10	10	5	5	5	84	Hi
Hsieh et al. (2002)	2	5	2	0	2	0	10	0	5	0	5	0	10	10	5	5	5	66	Med
Hurwitz et al. (2002, 2004, 2005) UCLA/Neck	2	5	4	0	2	12	10	5	0	0	5	0	10	0	5	0	5	65	Med
Hurwitz et al. (2002 and 2006). UCLA/LBP	2	5	4	0	4	12	10	5	0	0	5	0	10	0	5	0	0	62	Med
Jull et al. (2002)	2	3	2	3	4	0	10	0	0	5	5	0	10	10	5	5	5	69	Med
Nelson et al. (1998)	2	5	4	3	0	6	10	5	0	0	5	0	10	10	5	5	5	75	Hi
Plaugher et al. (2002)	2	2	0	3	0	0	10	0	5	0	5	0	10	0	5	0	0	42	Med
Santilli et al. (2006)	2	5	4	3	4	0	10	0	0	5	5	0	10	0	5	5	5	63	Med
Sawyer et al. (1999)	2	1	4	3	4	0	10	5	0	5	5	5	10	0	5	0	5	64	Med
Skargren et al (1997,1998)	2	5	4	3	4	12	5	5	2	0	0	0	10	0	5	5	5	67	Med
Strunk, Hondras (2008)	2	5	3	3	2	0	10	5	0	0	5	0	5	0	5	0	5	50	Lo
Tuchin et al (2000)	2	5	2	3	0	0	5	0	0	5	0	0	5	0	5	0	0	32	Lo
UK BEAM (2004)	2	5	4	0	0	12	10	5	0	5	0	0	10	10	5	5	5	78	Hi
Vicenzino et al (2001)	2	0	0	3	4	0	5	0	3	5	0	5	10	0	0	0	0	37	Lo
Williams et al. (2003)	2	5	4	2	0	6	10	5	0	5	5	0	10	0	5	5	5	69	Med

Appendix F. Nature and type of adverse events

Author and subject of Study	Definition of AEs	Type/Frequency	Onset	Duration	Severity/functional loss
Abbot N. et al. (1998) GP/public survey into adverse events of complementary and alternative medicine.	Direct adverse events "which might have been caused by the treatment administered" Serious direct effects defined as potentially life threatening or likely to cause death, disability or severe morbidity Non serious direct effects any other direct effect not designated serious. Indirect adverse effects that may have been caused by the wrong advice, prescription of an ineffective remedy for a treatable condition or disillusion with ineffective treatment.	As reported by GPs **Frequency:** Manual Therapy 28 direct 10 Indirect Direct effects most often associated with manipulative therapy 28/52 (54%) including unspecified "general manipulation 12/52 (23%) **Type:** Manipulation "Poor outcome" after manipulation to secondary cancer of neck.(1), CVA (1) Exacerbation of symptoms (4), Spinal cord compression (1), Paraplegia (2), Neurological damage (1) Nerve damage (1) CNS symptoms after cervical manipulation (1) Chiropractic, Paralysis (2) Severe pain (2), Slipped disc (1), Osteopathy, Exacerbation (4) Severe neck pain (1) Back injury (1), Fracture (2) Nerve damage (1) Headaches/giddiness (1) Paraparesis (1) Self reported adverse events Chiropractic 25 (4 confirmed by medical specialist) Osteopathy 22 (1 confirmed			

		by medical specialist) Physiotherapy 1 (1 confirmed by medical specialist)			
Adams G. et al. (1998) Survey of UK manual therapists towards manipulation and its complications		Cervical manipulation (21 patients/23 complications) Increased pain >than one day 7/23 (30%) Dizziness 3/23 (13%) Paraesthesia 3/23 (13%) Headache 2/23 (9%) Hearing loss 1/23 (4%) Vomiting 1/23 (4%) Petit mal 1/23 (4%) Oedema of arm 1/23 (4%) Patient angry/upset 1/23 (4%) Hypersensitivity 1/23 (4%) Unspecified 2/23 (9%) Thoracic manipulation (9 patients/12 complications) Increased pain >one day 8/12 (67%) Paraesthesia 1/12 (8%) Rib fracture 1/12 (8%) Loss/decreased muscle power 1/12 (8%) Autonomic problems 1/12 8%) Lumbar manipulation (7 patients/11 complications) Increased pain>one day 5/11 (45%) Referred pain 4/11(36%) Loss/decreased muscle power 1/11 (9%) Loss/decreased sensation 1/11 (9%)		Duration of 43 reported complications reported by 25 (19%) of users. 28 (65%) <1 week 15 (35%) >1 week Cervical manipulation Increased pain lasting more than one day 7/23 (30%) Thoracic manipulation Increased pain lasting more than one day 8/12 (67%) Lumbar manipulation Increased pain lasting more than one day 5/11 (45%)	
Assendelft W.J.et al (1996)		Complications of Spinal Manipulative Therapy. Vertebrobasilar 165/295			Outcomes of Spinal Manipulative Therapy. Aggregated figures of those

Complications of Spinal Manipulation a review of the literature		(51%) Other cerebral 13/295 (4%) Hernia and cauda equine 61/295 (19%) Other complications 56/295 (17%) 29 deaths reported in vertebrobasilar group			with vertebrobasilar symptoms Death 29/165 (17.6%) Residual Handicap 86/165 (52%) Complete Recovery 44/165 (26.7%) Unknown 6/165 (3.6%) Aggregated figures of those with vertebrobasilar symptoms who survived n= 136 (165-29) Residual Handicap 86/136 (63%) Complete Recovery 44/136 (32%) Unknown 6/136 (4%)
Barret A.J & Breen A.C (2000) Adverse effects of Spinal Manipulation within 48 hours post treatment	5 point Likert scale used to record patient self reported severity of symptoms “hardly any discomfort” “mild discomfort” “moderate discomfort” “severe discomfort” “worst possible discomfort”	No serious adverse events reported. Post treatment reactions At one hour (n=28). Extra pain 14(50%) Radiating pain 9 (32%) Stiffness 5 (18%) Dizziness 5 (18%) Tiredness 4 (14%) Headache 1 (4%) 1 Nausea 1 (4%) Vomiting 0 (0%) Other 0 (0%)	Post treatment reactions At one hour (n=28). Extra pain 14(50%) Radiating pain 9 (32%) Stiffness 5 (18%) Dizziness 5 (18%) Tiredness 4 (14%) Headache 1 (4%) 1 Nausea 1 (4%) Vomiting 0 (0%) Other 0 (0%)	Post treatment reactions At one hour (n=28), one morning (n=19) and two mornings (n=8) post treatment. Extra pain 14(50%) 7 (37%) 2 (25%) Radiating pain 9 (32%) 5 (26%) 4 (50%) Stiffness 5 (18%) 10 (53%) 5 (63%) Dizziness 5 (18%) 0 (0%) 2 (25%) Tiredness 4 (14%) 1 (5%) 0 (0%) Headache 1 (4%) 1 (5%) 0 (0%) Nausea 1 (4%) 0 (0%) 0 (0%) Vomiting0 (0%) 0 (0%) 0 (0%) Other 0 (0%) 4 (21%) 3 (38%)	Negative influence on activities of daily living At one hour (n=28), one morning (n=19) and two mornings (n=8) post treatment. Standing 6(22%) 6(32%) 4 (50%) Sitting 8 (29%) 8 (42%) 7 (88%) Walking 2 (7%) 8 (42%) 4 (50%) Sleeping 0 (0%) 4 (21%) 3 (38%)
Cagnie B. et al.	Patient self report of side	No serious side effects	60.5% reactions started 4	64% of reactions did not last	Patient self reported

(2004) Side effects of Spinal Manipulation after first visit (within 48 hours).	effects and difficulties in performing daily activities within 48 hours of manipulation (first visit)	reported. 283/465 (61%) reported at least one reaction of these 62.2% reported 2 or more side effects Headache 19.8% Stiffness 19.4% Aggravation of complaints 15.2% Radiating discomfort 12.1% Fatigue 12.1% Muscle spasm 5.8% Dizziness 4.3% Nausea 2.7% Others 9%	hours or< 4 hours post manipulation	more than 24 hours 19.4% of reactions lasted >48 hours	discomfort 14.3% slight 26.5% mild 39% moderate 21% severe 26.6% reported difficulties with activities of daily living (39% sport, 33% sleep, 46% work)
Carey P.F et al. (1993) Report on occurrence of CVA in chiropractic practice		13 reported CVAs No fatalities.			0/13 Death 1/13 (8%) complete quadriplegia 6/13 (46%) minor but permanent neurological damage 4/13 (25%) complete resolution 2/13 (15%) no physical disability but psychological problems
Dupeyron A. et al. (2003) Complications of vertebral manipulation		Radicular accidents 64 (69%) Cerebro vascular accidents 14 (15%) Medullary accidents 5 (5%) Other accidents 10 (11%) 35 radiculopathies (30 sciatic 5 crural) 29 cervicobrachial neuralgias 4 cauda equine 14 VCA (8 VBA, 4 ICADs, 2 unknown)			

		11 other (fractures, Horners, vertigo)			
Dvorak J.& Orelli F.V. (1985) Cervical spine manipulation, case reports and survey.		Complications following manipulation to the cervical spine Prevalence of types of AEs Vertigo 1218/1.53m (0.08%) Diminished consciousness 10/1.53m (0.0007%) Loss of consciousness 12/1.53m (0.0008%) Diminished consciousness and neurological symptoms 4/1.53m (0.00007%) Radicular deficits (C6,C7,C8) 11/1.53m (0.0007%) Complications following manipulation to the Lumbar spine In 140 cases pain was reported to have been worse than before manipulation. 9/140 had radicular symptoms 3/140 required surgery 1/140 had cauda equine symptoms			
Dvorak J. et al (1993) Survey of the Frequency of complications of manipulation of the spine.		No irreversible serious neurological complications reported Complications of cervical manipulation: 2 patients (1/75225 manipulations) reported loss of consciousness with complete recovery Complications of lumbar	Complications of Thoraco-lumbar manipulations: 175 patients (ratio of 1/1955 manipulations) reported immediate transitory increase in pain after manipulation of the lumbar spine.	Complications of Cervical manipulations: Overall incidence of transient side effects (eg disturbance of consciousness/radicular signs) was 1:16716 manipulations. 236 patients (1/637 manipulations) reported transient dizziness	

		manipulation: 9/17 (53%) patients (1/38013 manipulations) referred for surgery with verifiable disc herniation Complications of Thoraco-lumbar manipulations: 175 patients (ratio of 1/1955 manipulations) reported immediate transitory increase in pain after manipulation of the lumbar spine.		14 patients (1/10746 manipulations) reported transient loss of consciousness 6 patients (1/25075 manipulations) reported transient parathaesia in C6/7 dermatome 1 patient (1/150332) reported transient weakness in upper extremity Complications of Thoraco-lumbar manipulations: 17 patients (1/20125 manipulations) reported transient sensorimotor deficit and radicular symptoms.	
Dziewas R. et al. (2003) Cervical Artery Dissection, a study of outcome in 126 patients		1 death		At 6 month follow up 88 (70%) excellent recovery 22 (17%) mild to moderate handicap 15 (12%) severe handicap 1 (0.8%) fatality	
Egizii G. et al. (2005) Spinal manipulation a survey of French medical physicians.		26 adverse events post spinal manipulation Thoracic outlet phlebitis Disc pathology Neuralgias Myelopathies Myotomal Fracture Malaise Vertigo		17/26 (65%) < 24 hours 9/26 (35%) > 24 hours.	
Ernst E. (2007)		Reports Cagnie 61% at least			

Systematic Review of adverse effects of spinal manipulation		one AE Hurwitz(04) 30% at least one AE			
Gross A.R et al. (2007) Manipulation and mobilization for mechanical neck disorders	"Evidence of adverse effect" was used for trials that showed lasting negative changes.	Side effects were reported in 31% of the trials. They were benign,transient,and included headache, radicular pain, thoracic pain, increased neck pain distal paresthesia, dizziness, and ear symptoms.			
Haldeman S. et al. (2002a&b) Stroke, cerebrovascular ischaemia Cervical Artery Dissection and Cervical Spine Manipulation.		Neurological symptoms post cervical manipulation Nystagmus 30/64 (47%) Visual disturbances 43/64 (67%) Loss of coordination 52/64 81%) Hearing deficits/tinnitus 8/64 (13%) Numbness 37/64 (58%) Dizzy/vertigo/nausea/vomiting 50/64 (78%) Speech/swallowing dysfunction 44/64 (69%) Loss of consciousness 14/64 (22%) Death 2/64 (3%)	Onset of neurological symptoms associated with 64 CVAs Immediately 40/64 (63%) 5-30 mins 8/64 (13%) 1-12 hours 6/64 (9%) 13-23 hours 2/64 (3%) 1-2 days 4/64 (6%) 3-7 days 2/64 (3%) >1 week 1/64 (2%) Unknown 1 (2%)		Residual neurological deficit measured one year after CVA Complete recovery 8/44 (18%) Nystagmus 5/44 (11%) Visual disturbance 13/44 (30%) Loss of coordination 22/44 (50%) Hearing deficit/Tinnitus 1/44 (2%) Numbness 15/44 (34%) Dizzy/vertigo/nausea/vomit 10/44 (23%) Speech/swallowing dysfunction 14/44 (32%) Loss of consciousness 0 (0%)
Haldeman S. et al. (2002) Clinical Perceptions of risk of vertebral artery dissection after cervical manipulation		Total reported cases 43 Confirmed VAD 23/43 (53%) Transient Neuro symptoms 12/43 (28%) Reports of symptoms with alternative explanation 8/43 (19%)			
Hufnagel A. et al. (1999)		Neurological symptoms post manipulation (n=10 patients):	In 5/10 (50%) onset of symptoms was immediate. In 5/10 (50%) onset of		Outcome up to 4 years: No or mild deficits in 5/10 (50%).

Stroke following Chiropractic manipulation of the cervical spine.		Vertigo 7/10 (70%) Nausea 6/10 (60%) Vomiting 3/10 (30%) Cervico occipital pain 4/10 (40%) Brief syncope 2/10 (20%) Respiratory arrest and coma within minutes 1/10 (10%) Maximal neurological deficits severe in 9/10 (90%)	symptoms was within 2 days. Progression of neurological deficits occurred within the following hours to a maximum of 3 weeks		Marked deficits in 3/10 (30%). Persistent locked in syndrome in 1/10 (10%). Persistent vegetative state in 1/10 (10%).
Hurwitz EL. et al. (1996) Manipulation and Mobilisation of the Cervical Spine. Systematic Review		Death 18%(21) Wallenberg's syndrome 20% (23) Cerebral/cerebellar infarct 36% (42) Vertebral artery spasm/dissection 15%(18) Locked in syndrome 2%(3) Other/unknown 27%(32)	First symptoms: During therapy 13% (15/118) Within seconds 57% (67/118) Within 24 hours 22%(26/118) Later 8%(10/118)		No/minimal impairment 36%(42) Major residual symptoms 43%(51)
Hurwitz EL. et al. (2004/5 Chiropractic care of neck pain.	6 categories: 1) Increased neck pain,stiffness,soreness. 2) Radiating pain or discomfort. 3) Tiredness/fatigue. 4) Headache 5) Neurologic symptoms 6)Any other adverse symptom 11 point patient discomfort rating scale: Neck Disability Index (0-50) measuring pain and disability in first 2 weeks post treatment: Pain and disability assessments up to 26 weeks post treatment.	n=280 Patients Neck symptoms 70/280 (25%) Radiating symptoms 17/280 (6.1%) Tiredness/fatigue 28/280 (10%) Headache 44/280 (15.7%) Dizziness/imbalance 9/280 (3.2%) Nausea/vomiting 5/280 (1.8%) Visual deficit 4/280 (1.4%) Hearing deficit 6/280 (2.1%) Limb weakness 7/280 (2.5%) Confusion/disorientation 4/280 (1.4%) Depression/Anxiety 6/280 (2.1%)	Onset 24or<24 hours All symptoms 171/212 (80.7%) Neck symptoms 57 (81.4%) Radiating symptoms 12 (70.6%) Tiredness/fatigue 24 (85.7%) Headache 37(84.1%) Dizziness/imbalance 8 (88.9%) Nausea/vomiting 4 (80.0%) Visual deficit 3 (75.0%) Hearing deficit 4 (66.7%) Limb weakness 5 (71.4%) Confusion/disorientation 2 (50.0%) Depression/Anxiety 4 (66.7%) Manipulation vs	Duration >24hours All symptoms 82/212 (38.7%) Neck symptoms 30 (42.9%) Radiating symptoms 8 (47.1%) Tiredness/fatigue 12 (42.9%) Headache 15 (34.1%) Dizziness/imbalance 3 (33.3%) Nausea/vomiting 0 (0%) Visual deficit 3 (75.0%) Hearing deficit 2 (33.3%) Limb weakness 2 (28.6%) Confusion/disorientation 1 (16.7%) Depression/Anxiety 3 (50.0%) Manipulation vs	Effect on ADLs "A little" All symptoms 87/212 (41%) Neck symptoms 29 (41.4%) Radiating symptoms 7 (41.2%) Tiredness/fatigue 14 (50.0%) Headache 18 (40.9%) Dizziness/imbalance 4 (44.4%) Nausea/vomiting 3 (60.0%) Visual deficit 2 (50.0%) Hearing deficit 0 (0%) Limb weakness 2 (28.6%) Confusion/disorientation 0 (0%) Depression/Anxiety 2 (33.3%)

			mobilisation Onset <24 hours Neck pain, stiffness Manip 79.5% Mob 83.9% Radiating pain/discomfort Manip 77.8% Mob 62.5% Tiredness/fatigue Manip 94.1% Mob 72.7% Headache Manip 95.5% Mob 72.7% Dizziness/imbalance Manip 100% Mob 66.7% Fainting Manip 0% Mob 0% Nausea/vomiting Manip66.7% Mob 100% Visual deficit Manip 75.0% Mob 0% Hearing deficit Manip 80.0% Mob 0% Limb weakness Manip 75.0% Mob 66.7% Confusion/disorientation Manip 50.0% Mob 50.0% Depression/anxiety Manip 66.7%.Mob 66.7% 30% reported at least 1 ae in the first 2 weeks 80% of symptoms began within 24 hours of treatment	mobilization Frequency at 2 week follow up Neck pain, stiffness Manip27.7% Mob 22.3% Radiating pain/discomfort Manip 6.4% Mob 5.8% Tiredness/fatigue Manip 12.1% Mob 7.9% Headache Manip 15.6% Mob 15.8% Dizziness/imbalance Manip 4.3% Mob 2.2% Fainting Manip 0% Mob 0% Nausea/vomiting Manip2.1% Mob 1.4% Visual deficit Manip 2.8% Mob 0% Hearing deficit Manip 3.5% Mob 0.7% Limb weakness Manip 2.8% Mob 2.2% Confusion/disorientation Manip 1.4% Mob 1.4% Depression/anxiety Manip 2.1%2.Mob 2.2%	"A lot" All symptoms 40/212 (18.9%) Neck symptoms 13 (18.6%) Radiating symptoms 6 (35.3%) Tiredness/fatigue 6 (21.4%) Headache 9 (20.5%) Dizziness/imbalance 0 (0%) Nausea/vomiting 0 (0%) Visual deficit 0 (0%) Hearing deficit 0 (0%) Limb weakness 3 (42.9%) Confusion/disorientation 1 (25.0%) Depression/Anxiety 1 (16.7%) Majority of symptoms gone within 24 hours of onset and did not appreciably affect daily activities
Klougart N. et al.(Part 1) (1996) Occurrence of Cerebrovascular Accidents after manipulation to the neck.		5 cases of CVA identified. 1 resulted in death. 4 resulted in permanent neurological sequelae of varying severity 4/5 Dizziness, 1 headache, 4/5 nausea/vomiting, 2 respiratory distress, 2 hearing deficits, 1 facial paralysis, 1 speech	4/5 immediate (80%) 1/5 10 minutes (20%)		

		disturbance, 1 gait disturbance, 2 parasthesias, 1 dilated pupil, 1 reduced strength			
Klougart N. et al .(Part 2) (1996) Occurrence of Cerebrovascular Incidents and treatment of the upper neck.	Cerebrovascular incident defined as a transitional sign of possible cerebrovascular accident.	Vertigo 10/22 (45%) Loss of consciousness 9/22 (41%) Nausea 7/22 (32%) Cramps 6/22 (27%) Falling 3/22 (14%) Nystagmus 3/22 (14%) Vomiting 3/22 (14%) Ataxia 3/22 (14%) Parasthesia 3/22 (14%) Rales 2/22 (9%) Blanching 2/22 (9%) Fatigue 2/22 (9%) Headache 2/22 (9%) Visual disturbance 1/22 (4.5%) Dyspnea 1/22 (4.5%) Cold 1/22 (4.5%) Contracted pupil 1/22 (4.5%) Ptosis 1/22 (4.5%) Loss of bladder control 1/22 (4.5%) Dysphagia 1/22 (4.5%) No information 1/22 (4.5%)	Immediately 13/22 (9%) < 1 hour 4/22 (18%) >24 hours 1/22 (5%) Undetermined 4/22 (18%)	<1 hour 6/22 (27%) <24 hours 6/22 (27%) >24 hours 5/22 (23%) Undetermined 5/22 (23%) 54% <24 hours	
Leboeuf-Yde C. et al. (1997) Side effects of chiropractic treatment	Distinction between common and uncommon reactions	3 groups of reactions: (approx 66%) local reactions (approx10%) pain outside area of treatment/fatigue/headache (<5%) nausea/dizziness/other Other includes Foot pain/cramp Pulling sensation in limbs Trembling in groin Rumbling in stomach	Same day 58% Next day 33% Later 4% Don't know 1% No response 4%	Few hours only 21% Up to 24 hours 34% Between 24-48 hours 19% >48 hours 19% Don't know 1% No response 6% 55% up to 24 hours	Description of discomfort Moderate 35% Light 33% A fair bit 20% A lot 8% Very much 4% Affect of discomfort on activities at home/work Not at all 57% Somewhat 26% A fair bit 8%

		Pressure in head Difficulty in falling asleep			A lot 1% Don't know 1% No response 7%
Lee K.P. et al. (1995) Neurologic complications of chiropractic manipulation of the cervical,thoracic and lumbar spine.	Outcome categories: No deficits Mild,marked,severe, death,unknown within 24 hours of manipulation and 3 month follow up.	102 neurologic complications 56/102 (55%) stroke 16/102 (15.7%) myelopathies 30/102 (29.4%) radiculopthies			Persistent deficits 3 month after onset: Stroke 86% Myelopathy 88% Radiculopathy 97% Patients with persistent disability who had severe deficits at three months: Stroke 46% Myelopathy 57% Radiculopathy 55% Severity of clinical deficit 3 months following onset of neurological complications. Stroke: No deficit 8 (14%) Mild deficit 26 (46%) Moderate deficit 12 (21%) Severe deficit 9 (16%) Myelopathy: No deficit 2 (13%) Mild deficit 6 (38%) Moderate deficit 5 (31%) Severe deficit 3 (5%) Radiculopathy: No deficit 1(3%) Mild deficit 13 (43%) Moderate deficit 15 (50%) Severe deficit 1 (3%)
Malone D.G.et al. (2002) Case series of 22 patients with complications of cervical spine manipulation.	Adverse effect: Any detrimental result of treatment. Adverse reaction: A slight or clinically insignificant/short lived symptom. Adverse incident: unexpected irreversible impairment	No deaths reported. 21/22 underwent surgery. Radiculopthy 21 Myelopathy 11 Brown-Sequard syndrome 2 Vertebral Artery occlusion 1 Analysis of 1995 census data			

	injury/fatality	(Tulsa USA). 32/172 Worsening symptoms 21/172 irreversible complications 20/172 worsened radiculopathy 11/172 worsened myelopathy 1/172 new onset vertebrobasilar TIA			
Magarey M.E. et al. (2004) Review of pre-manipulative testing of the cervical spine.		291 types of effects within past 2 years. Vertebrobasilar symptoms account for 94.4% (dizziness diplopia dysphagia drop attacks nausea) No reported major complications. No CVAs reported.			Of those patients with adverse events 15.9% required medical attention while remainder resolved without intervention
Michaeli A. (1993) Complications of manipulative physiotherapy to cervical spine		Manipulation 52 post manipulative complications in 29 patients: (4/52 post thoracic/lumbar manipulation 48/52 post cervical manipulation) Post cervical manipulation: Dizziness 25% (12/48) Severe Headache 21% (10/48) Nausea 23% (11/48) Blurred vision 6% (3/48) Vomiting 6% (3/48) Nystagmus 6%(3/48) Cerebral Vascular accident 0% Loss of consciousness 2% (1/48) Clamminess of skin 0%		Complications from cervical manipulation <30minutes1/25 (4%) 1-12 hours 5/25 (20%) 1-3 days 12/25 (48%) 1 week 5/25 (20%) 6-12 weeks 2/25 (8%) 2 years 0 (0%) Average recovery period 6.3 days. < 72 hours 18/25 (72%) Complications from cervical mobilisation <30minutes 12/48 (25%) 1-12 hours 24/48 (50%) 1-3 days 10/48 (21%) 1 week 1/48 (2%) 6-12 weeks 0/48 (0%) 2 years 1/48 (2%) <72 hours 46/48 (96%) Complications from	State of recovery from complications of cervical manipulation Total 25/25 (100%) State of recovery from complications of cervical mobilization. Total 47/48 (98%) Partial 1/48 (2%)(Patient suffered CVA) State of recovery from complications of cervical mobilisation with brachialgia Total 6/10 (60%) Partial 2/10 (20%) None 2/10 (20%)

		Brachialgia 6% (3/48) Brachialgia with neurological deficit 2% (1/48) Increased pain >2weeks 0% Acute wry neck 2% (1/48) Mobilisation 129 post mobilisation complications in 58 patients Dizziness 30% (39/129) Severe Headache 27% (35/129) Nausea 22% (28/129)) Blurred vision 4% (5/129) Vomiting 3% (4/129) Nystagmus 2% (3/129) Cerebral Vascular accident 1% (1/129) Loss of consciousness 0% Clamminess of skin 1% (1/129) Brachialgia 3% (4/129) Brachialgia with neurological deficit 5% (6/129) Increased pain >2weeks 2% (3/129) Acute wry neck 0%		cervical mobilisation with brachialgia <30minutes 0/10 (0%) 1-12 hours 2/10 (20%) 1-3 days 4/10 (40%) 1 week 0/10 (0%) 6-12 weeks 4/10 (40%) 2 years 0/10 (0%)	
Oppenheim J.S. et al. (2005) Nonvascular complications following spinal manipulation	Qualitative neurological change in symptoms during treatment (not included if increased severity of presenting symptoms)	3 died from unrecognized malignancies (pathologic fractures from metastatic tumours in vertebral bodies) 27 symptoms reported (n=18 patients) Paraparesis 2/27 (7%) Myelopathy 4/27 (15%) Central cord syndrome 4/27 (15%) Cauda Equina Syndrome 2/27 (7%)			

		Radiculopthy 8/27 (30%) Foot drop 2/27 (7%) Quadriparesis 2/27 (7%) Weak Biceps 1/27 (4%) Sensory deficit 2/27 (7%)			
Reuter U. et al. (2006) Vertebral Artery Dissection post chiropractic neck manipulation.		1 death 1 vegetative state Vertebrobasilar symptoms 56% (2/36) Focal neurological deficit 89% (32/36) New head/neck pain 22% (8/36) Progression of symptom 14% (5/36) Impaired consciousness 11% (4/36)	Within session 14% (5) <60 mins 12%(4) 1-6hrs 14% (5) 6-12hrs 20% (7) 12-48hrs 5%(14) >48hrs 24%(9)		
Rivett D.A. & Milburn P. (1997) Complications from Spinal Manipulation		Cervical complications: n=26 0 Deaths CVA 14 Radiculopathy 7 Disc prolapse 3 Increased pain 2 Thoracic complications: n=6 Myelopathy 3 Fracture 1 Disc prolapse 1 Increased pain 1 Lumbar complications: n=10 Radiculopthy 3 Disc prolapse 3 Disc prolapse and radiculopathy 3 Unknown 1			7 of CVA cases permanently disabled 9 of CVA cases recovery incomplete Outcomes Long term adverse effects 43% Spontaneous resolution 4 Resolution with intervention 19 Improving 1 Incomplete resolution 2 Permanent disability 16
Rubinstein SM. et al. (2007/8) Chiropractic care of neck pain.	Symptoms thought to be associated with adverse events measured at 2nd and 4th visit using 11 point Numerical Rating Scale	No serious adverse events recorded. At 2nd/4th visit Local pain/stiffness to treated area:29.1%/1.5%	48% indicated a new/related or worsening of the presenting or existing complaint following first visit 26% indicated an adverse	At 2nd/4th visit Local pain/stiffness to treated area:29.1%/1.5% Pain>30% in the 24 hours preceding the	High intensity Adverse events: 14% after 1st visit 15% after2/3rd visit but none worse at 12month follow up.

	Definitions: Adverse event defined as a new complaint not present at baseline or >30% worsening of existing complaint. Intense Adverse event scored≥8 on NRS Serious Adverse event defined as resulting in death, was life threatening necessitated admittance to hospital or caused disability	Pain>30% in the 24 hours preceding the visit:22.0%/18.6% Distant pain/stiffness to treated area19.6%/2.4% Headache10%/2.8% Radiating pain -%/2% Tiredness/Sleepiness7.7%/1.7% Dizziness/light headedness7.5%/1.3% Nausea5.5%/1.7% Ringing in ears3.7%/0.9% Confusion/Disorientation 2.8%/1.3% Fear/depression1.8%/0.4% Other 2.6%/2.0%	event following 2nd or 3rd visit At 2nd visit 90% indicated that adverse event began within 2 days of treatment 56% at least one adverse vent after any of first three treatments and 13% reported events to be severe Most common adverse events reported at 2nd and 4th were musculoskeletal or pain related. 72% after 1st visit 75% after2nd/3rd visit Nausea/psychological symptoms overall <8% but 19% reported at least one non musculoskeletal event in any of first three treatments.	visit:22.0%/18.6% Distant pain/stiffness to treated area19.6%/2.4% Headache10%/2.8% Radiating pain -%/2% Tiredness/Sleepiness7.7%/1.7% Dizziness/light headedness7.5%/1.3% Nausea5.5%/1.7% Ringing in ears3.7%/0.9% Confusion/Disorientation 2.8%/1.3% Fear/depression1.8%/0.4% Other 2.6%/2.0%	Those who reported adverse events (14% at 2nd visit/15% at 4th visit) perceived event to have been severe in intensity. Most who reported adverse events (85% at 2nd visit/81% at 4th visit) perceived event to have no to minor influence on activities of daily living
Senstad O. et al. (1996) Side Effects Chiropractic Spinal Manipulative Therapy.	Unpleasant reactions reported by patients	n=95 patients Serious incidents 0% No discomfort 68% Some overall discomfort 34% Local discomfort 19% Radiating discomfort 4% Tiredness 4% Headache 4% Dizziness 2.5% Nausea 0.25% Heat in skin 0.25%	Same day as ttt 87% Immediate 14% < 60mins 42% Duration: <24hours 83% <12hours 55% <4hours 23% 24-48 hours 11% 48-72 hours 6%	< 4hours 23% <12hours 55% < 24hours 83% 24-48 hours 11% 48-72 hours 6%	"Moderate discomfort" 50% "Slight discomfort" 40% "Very noticeable discomfort" 10% Ability to work reduced reported in 14% Not known if inability to work a result of treatment or therapist instructions.
Senstad O.et al. (1996) Predictors of side effects to Spinal ManipulativeTherapy.	Patient self reported reactions, based on frequency of occurrence divided into "common" and "uncommon" reactions.	14 episodes of "unbearable discomfort" Adverse reactions more common after first treatment. 40% at 1st vs 13% at 6th treatment Common reactions: Local discomfort Headache	Of 9/14 episodes of "unbearable discomfort" occurred within first two treatment sessions. Adverse reactions more common after first treatment. 40% at 1st vs 13% at 6th treatment		14 cases of "unbearable discomfort" reported by 12 patients. 7/14 (50%)Headache 9/14 (64%) Symptoms of long duration 3/12 (25%) (all female) reported one event each of

		Tiredness Radiating discomfort Uncommon reactions: Dizziness Nausea Hot skin "Other"			reduce daily activities after treatment.
Senstad O. et al. (1997) Side effects of Spinal Manipulative Therapy.		No severe incidents reported throughout study. Local discomfort 53% Headache 12% Radiating discomfort 10% Dizziness 5% Nausea 4% Hot skin 2% Other 2% Others include: Altered sensitivity Skin rash Gastro intestinal symptoms Psychological symptoms Symptoms in the ears Musculoskeletal symptoms including cramp, pain and stiffness.	<=10 minutes 198(17%) 10minutes-4 hours 556(47%) >4hours 373 (32%) Not stated 47(4%)	Reactions disappeared During day of treatment 864 (74%) During day 2 183 (16%) During day 3 or later 81 (7%) Not stated 48 (4%) 64% of reactions started within 4 hours 74% disappeared within 24 hours 90% disappeared within 48 hours	35% of reactions characterized as "mild" 50% of reactions characterized as "moderate" 14% of reactions characterized as "definitely unpleasant" 1% of reactions characterized as "unbearable" 11% could not perform daily activities because of reactions.
Shekelle P.G. et al. (1992) Spinal Manipulation for Low Back Pain a Literature Review		"No complications were reported in the clinical trials of manipulation, which in total comprised more than 1500 patients treated with manipulation." P 591			
Terret A.G. (1987) Vascular Accidents from Cervical Spine Manipulation a report on 107 cases	Vascular accident	26 fatalities 6 tetraplegia (two included in fatalities) 36 neurological deficit 2 intellectual/memory deficit 3 residual deafness 1 Barre-Lieou syndrome 2 hearing loss and tinnitus 1 hearing loss and			10 almost complete recovery 11 complete recovery 1 unknown but survived 30 years 7 unknown

		nystagmus 1 hearing loss and residual facial paresis			
Thiel H. et al. 2007 and 2008) Safety of Chiropractic Manipulation of the Cervical spine	Serious adverse event defined as necessitating referral to hospital (accident and emergency) and/or severe onset/worsening of symptoms immediately after treatment and/or resultant persistent or significant disability/incapacity. Minor adverse event defined as a worsening of presenting symptoms or onset of new symptoms up to 7 days after treatment.	No reports of serious adverse events. Highest risk immediately post treatment was fainting/dizziness/light headedness at worst 16/1000 consultations Immediate worsening of presenting symptoms per treatment consultation (n=28,109) Neck pain 1.72% Shoulder/arm pain 1.00% Reduced neck/shoulder/arm movement/stiffness 0.62% Headache 0.42% Facial pain/numbness/tingling 0.08% Numbness/tingling in upper limbs 0.40% Upper/mid back pain 0.71% Lower limb numbness tingling 0.03% Fainting/dizziness/light headedness 0.34% Ringing in ears/tinnitus 0.03% Nausea/vomiting 0.06% Visual problems 0.08% Other 0.11% Immediate onset of new symptoms per treatment consultations (n=28,109) Neck pain 0.40% Shoulder/arm pain 0.20% Reduced neck/shoulder/arm movement/stiffness 0.30%	Highest risk immediately post treatment was fainting/dizziness/light headedness at worst 16/1000 consultations Immediate worsening of presenting symptoms: Neck pain 1.72% Shoulder/arm pain 1.00% Reduced neck/shoulder/arm movement/stiffness 0.62% Headache 0.42% Facial pain/numbness/tingling 0.08% Numbness/tingling in upper limbs 0.40% Upper/mid back pain 0.71% Lower limb numbness tingling 0.03% Fainting/dizziness/light headedness 0.34% Ringing in ears/tinnitus 0.03% Nausea/vomiting 0.06% Visual problems 0.08% Other 0.11% Immediate onset of new symptoms: Neck pain 0.40% Shoulder/arm pain 0.20% Reduced neck/shoulder/arm movement/stiffness 0.30% Headache 0.45% Facial pain/numbness/tingling 0.16% Numbness/tingling in upper	Up to 7 days post treatment headaches at worst 4/100 consultations Up to 7 days post treatment upper limb numbness/tingling at worst 15/1000 consultations. Up to 7 days post treatment fainting/dizziness/light headedness at worst 13/1000 consultations. At follow up the onset of new or worsening presenting symptoms the most common was Discomfort in the area of manipulation 7.31% (Cervical) Shoulder/arm pain 4.78% Reduced neck/shoulder/arm movement/stiffness 3.94	

		Headache 0.45% Facial pain/numbness/tingling 0.16% Numbness/tingling in upper limbs 0.33% Upper/mid back pain 0.18% Lower limb numbness tingling 0.11% Fainting/dizziness/light headedness 1.45% Ringing in ears/tinnitus 0.13% Nausea/vomiting 0.11% Visual problems 0.18% Other 0.39% Onset of new or worsening of presenting symptom in follow up period (7days) (n=15,520) Neck pain 7.31% Shoulder/arm pain 4.78% Reduced neck/shoulder/arm movement/stiffness 3.94% Headache 3.90% Facial pain/numbness/tingling 0.39% Upper limb numbness/tingling 1.27% Upper/mid back pain 2.51% Lower limb numbness tingling 0.33% Fainting/dizziness/light headedness 1.11% Ringing in ears/tinnitus 0.32% Nausea/vomiting 0.59% Visual problems 0.21% Other 1.9%	limbs 0.33% Upper/mid back pain 0.18% Lower limb numbness tingling 0.11% Fainting/dizziness/light headedness 1.45% Ringing in ears/tinnitus 0.13% Nausea/vomiting 0.11% Visual problems 0.18% Other 0.39% Onset of new or worsening of presenting symptom in follow up period (7days): Neck pain 7.31% Shoulder/arm pain 4.78% Reduced neck/shoulder/arm movement/stiffness 3.94% Headache 3.90% Facial pain/numbness/tingling 0.39% Upper limb numbness/tingling 1.27% Upper/mid back pain 2.51% Lower limb numbness tingling 0.33% Fainting/dizziness/light headedness 1.11% Ringing in ears/tinnitus 0.32% Nausea/vomiting 0.59% Visual problems 0.21% Other 1.9%		
Vohra S. et al. 2007)	Severe (hospitalization,	14 cases of direct adverse	10/14 (71%) onset of		

A Systematic Review of adverse events associated with Pediatric Spinal Manipulation	permanent disability, mortality). Moderate (transient disability,involving medical care not hospitalisation). Minor (self limiting not requiring medical care). Indirect (delayed diagnosis or treatment of a medical condition)	events involving neurologic or musculoskeletal events. 9 Severe 2 Moderate 3 Minor 20 Indirect (7 involved delayed treatment of cancer and diabetes 3 resulted in death, 2 from Meningitis, 1 from embryonal rhabomyosarcoma).	adverse events within 24 hours		

Appendix G. Main table showing origin of research

Author	"Origin"	Author	"Origin"	Author	"Origin"	Author	"Origin"
Abbot N et al (1998)	Academic Research	Dvorak J., Orelli F. (1985)	Neurologist	Hurwitz E. et al (1996)	Chiro	Rubinstein S. M. et al (2008)	Chiro
Adams G et al (1998)	Physio	Dvorak J. et al (1993)	Neurologist	Hurwitz E. et al (2004)	Chiro	Rubinstein S. M. et al (2007)	Chiro
Anderson-Peacock E.et al (2005)	Chiro	Dziewas R. et al (2003)	Neurologist	Hurwitz E.et al (2005)	Chiro	Rubinstein S.M. et al (2005)	Chiro
Assendelft W. J. et al (1996)	Medical Doc	Egizii G. A. (2005)	Physical Medicine	Klougart N. et al (1996) Part I	Chiro	Senstad O. et al (1996) (a)	Chiro
Barrett A. J., A. C. Breen (2000)	Chiro	Ernst E. (2001)	Academic Research	Klougart N. et al (1996) Part II	Chiro	Senstad O. et al (1997)	Chiro
Boyle E. et al (2008)	Chiro	Ernst E. (2007)	Academic Research	Leboeuf-Yde C. et al (1997)	Chiro	Senstad O. et al (1996) (b)	Chiro
Bronfort G. et al (2001)	Chiro	Garner M. J. (2007)	Chiro	Lee K. P. et al (1995)	Neurologist	Shekelle P. G. et al (1992)	Chiro
Cagnie B. et al (2004)	Physio	Gross A. et al (2007)	Cochrane review	Malone D. G. et al (2002)	Medical Doc	Smith W. S.et al (2003)	Neurologist
Carey P. F. (1993)	Chiro	Haldeman S.et al (1999)	MD/Chiro	Margarey M. (2004)	Physio	Terrett A. G. (1987)	Academic
Cashley M. et al (2008)	Chiro	Haldeman S.et al (2002) (a)	MD/Chiro	Mascalchi M. et al (1997)	Neurologist	Thiel H. W.et al (2007)	Chiro
Cassidy J. D et al (2008).	Chiro	Haldeman S. et al (2002) (b)	MD/Chiro	Michaeli A. (1993)	Physio	Thiel H.W. et al (2008)	Chiro
Coulter I. (1998)	Chiro	Haldeman S.et al (2002) (c)	MD/Chiro	Oliphant D. (2004)	Chiro	Vohra et al (2007)	Chiro
Dabbs V. (1995)	Chiro	Hancock M.J. et al (2007)	Academic Research	Oppenheim J. S et al (2005)	Medical doc		

di Fabio R. (1999)	Physical Therapy	Haneline M. T. et al (2003)	Chiro	Rivett D., Milburn P. (1997)	Physio		
Dittrich D.et al (2007)	Neurologist	Haneline M. T.et al (2005)	Chiro	Reuter U.et al (2006)	Neurologist		
Dupeyron A. et al (2003)	Physical medicine	Hufnagel A. et al (1999)	Neurologist	Rothwell D.et al (2001)	Medical		