3.0 Methodology

This section is dedicated to explaining the method by which research papers were searched, selected, analysed and evaluated to ensure all available relevant studies have been located and quality assessed. Quality assessment of each individual report was carried out using the Jadad 3-item quality assessment scale to assess control of factors of bias.

3.1 Search Strategy: Keywords

The word “chromium” is an essential text-word to search, as this returns studies which concentrate on the supplementation of the trace element, chromium. There are no other synonyms of chromium, except the symbol, Cr, may occasionally have been used. The non-toxic, trivalent, form is the most commonly studied and is written as Cr^{+3}, other forms are 0, +2 and +6 (toxic, hexavalent form). Chromium is most commonly studied in the synthetic form Chromium Picolinate (CrPic), however, other forms include chromium nicotinate (CrNic), chromium chloride (CrChl) and chromium yeast.

Wilczynski and Haynes (2003) conducted a study into optimising search strategies for detecting clinically sound causation studies in MEDLINE (International literature database). Wilczynski et al. (2003) found that specificity, defined as the proportion of low quality articles not retrieved, could be achieved using a single term. However, using a combination of terms, as many as three or more, enhanced sensitivity (>93%), defined as proportion of high quality articles for a particular topic retrieved, as well as specificity

(>94%), precision (>4%), defined as proportion of retrieved articles of high quality, and accuracy (>94%), defined as the proportion of all articles correctly classified. Wilczynski et al. (2003) also recommended using alternative words and terms to broaden the search. For this the authors used their own knowledge of the topic, the Medical Subject Headings (MeSH) on-line vocabulary and interviews of clinicians and librarians to compile a list of keywords to search. The following MeSH (acquired from the United States National Library of Medicine, 2007) and alternative text-words (exact words authors use in titles and abstracts) for chromium, physical performance, body composition, metabolism and health risk can be found in Table 1.

Table 1 – Chromium, Body Composition and Physical Performance Associated and Related Keywords and Text-words

Chromium	Body Composition	Physical Performance
Cr	Lean Body Mass	Endurance
Cr Picolinate	Fat Mass	Strength
Cr Nicotinate		
Cr Chloride		

3.2 Search Methodology

The individual search protocols for studies into chromium and body composition, physical performance, metabolism and health are described below. Each part of the protocol has been carried out so that a variety of key text-words can be incorporated in the search. As a rule, if a search yields more than five-hundred articles it was assumed that the specificity of the search term is too low for the particular search engine / database. For this reason, the search protocol is designed to increase in specificity as the investigator progresses through the process.

Chromium and Body Composition Search Protocol

1. Primary search term: chromium AND body composition
2. Secondary search terms: chromium AND lean body mass
   chromium AND fat mass
3. Tertiary search terms:
   chromium AND body composition AND lean body mass AND fat mass

Chromium and Physical Performance Search Protocol

1. Primary search term: chromium AND physical performance
2. Secondary search terms: chromium AND strength
   chromium AND endurance
3. Tertiary search terms:
   chromium AND body composition AND lean body mass AND fat mass

These keywords have been combined using Boolean search operators. This involves the use of the word “AND”, “OR” and bracket [(…)] to refine the search. Keywords were required to find studies associated with lean body mass, fat mass and physical performance. Wildcard search words were created using an asterix (*). For example, insulin potentiat* could be entered to search for insulin potentiate, potentiator and potentiation.

3.3 Journal and Database Searches

The search terms described were used in a variety of general and literature dedicated search engines. The procedure, beginning with powerful search engines starts the process followed by journal databases with access to fewer journals and finally searches within specific journal titles.

1. **Pubmed** (www.ncbi.nlm.nih.gov)

   A service of the U.S. National Library of Medicine and the National Institute of Health that includes over 17 million citations from MEDLINE and other life science journals for biomedical articles back to the 1950s. Pubmed provides the most citations, but provides general results.

2. **Google** (www.google.co.uk)

   A powerful web search engine. Will retrieve numerous non-peer reviewed Web sites, but will also retrieve journal articles, particularly through the Google Scholar option, which may not have been located via the previous method.

3. **ScienceDirect** (www.sciencedirect.com)

   ScienceDirect is an online journals service from Elsevier B. V., to which the University of Chester has access to over 1500 full text scientific, technical and medical research journals.

4. **Blackwell Synergy** (www.blackwell-synergy.com)

   Blackwell Synergy is the online journals service from Blackwell Publishing, to which the University of Chester has access to over 600 full-text journals.

5. **Specific Journals**

   Individual publications specific to the areas research covered by this systematic review such as supplementation, sports nutrition, metabolism, and strength/endurance training were searched. The benefit of searching an individual journal using only the primary search terms may retrieve studies not found in the more general searches used above. The list of journals to search individually include:

   - American Journal of Clinical Nutrition
   - Diabetes
   - Diabetes Care
   - International Journal of Sport Nutrition and Exercise Metabolism
   - Journal of Applied Physiology
   - Journal of Strength and Conditioning Research
   - Medicine and Science in Sports and Exercise
   - Metabolism

6. **Relevant searches use Pubmed or equivalent "related articles"**

   The final technique in retrieving articles is to use the "related articles" link. Pubmed displays this link next to all article titles. The related articles link is an effective way of expanding a literature search using relevant studies as search templates.

3.4 Article Retrieval

Once articles of interest have been identified the process of retrieval of the full-text article is employed. A selected few, often articles of importance or particular interest and subscription free journals, allow on-line access to full-text articles through the Pubmed database. For the majority of articles subscription to the journals is necessary and were retrieved by other methods. The University of Chester (www.chester.ac.uk) subscribes to over 7,000 E-journals (online, electronic journals). A search of the electronic resources catalogue often locates the required journal. If the above two options have been exhausted, the final option is to request the article through the Inter Library Loans service, which provides a copy from the British Libraries Document Supply Centre (Boston Spa, West Yorkshire).

3.5 Article Selection and Exclusion

For the article to be valid to the literature review, the study must satisfy the following criteria:

a) Chromium supplementation must be included in the study
b) Study must be conducted on human subjects
c) Full study report must be provided (abstracts unacceptable for review)
d) Studies must be written in the English language
e) The dose and duration of chromium supplementation must be described
f) The type and frequency of training must be described (if any)
g) Healthy subjects must be used, unless stated otherwise, e.g. non-diabetic patients
h) Controlling of bias is adequate, e.g. double-blinding, randomisation

Studies which satisfy all of the above selection criteria were eligible for inclusion in the review. Studies which do not satisfy one or more of the above criteria were excluded as either the content of the study was inappropriate or the paper lacked essential information which was required for adequate analysis. Studies which were not selected for use in the main review were mentioned in brief, on condition the study provides useful information to stimulate the debate regarding the efficacy of chromium supplementation.

3.6 Article Quality Assessment

Moher et al. (1995) assessed twenty-five scales and nine checklists developed to assess the quality of randomised controlled trial reports. The authors created an annotated bibliography for each scale and checklist reviewed and concluded that all the scales reviewed showed major weaknesses in aspects of development, methodology and reliability, the only exception being the Jadad scale. Moher et al. (1995) may be biased, as one of the principal authors of the report was also the developer of the Jadad scale. The largest criticism of all the scales, with the exception of the Jadad scale, was the absence of any explanation of how each of the scales were developed.

In 1996, Jadad et al. published a report describing the development of an instrument to assess the quality of reports of randomised clinical trials in pain research and its use to determine the effect of rater blinding on the assessments of report quality. Jadad et al. (1996) enlisted the help of six judges to develop an 11-item instrument for quality assessment, which was used to score thirty-six research papers (seven previously judged excellent, six as poor and the remaining twenty-three were chosen randomly). Further to this, Jadad et al. (1996) blinded seven of the fourteen raters to the author's names and affiliation, the names of journals, the date of publication, the sources of financial support for the study, and the acknowledgements. Finally, Jadad et al. (1996) had each rater use an 11-item, 6-item (items with adequate frequency of endorsement) and 3-item (directly related to the control of bias) scales to assess all thirty-six reports.

Jadad et al. (1996) found that the inter-rater agreement using either the 11-, 6- or 3-item scales were high, with the 3-item scale showing the highest levels of agreement (0.66), the general trend showing an increase in inter-rater agreement as the number of items in the scale were reduced. Construct validity was also good, with reports previously judged as excellent scoring significantly ($p < 0.001$) higher than randomly selected and poor study reports. Randomly selected reports also scored significantly ($p < 0.001$) higher than the previously judged poor study reports. Jadad et al. (1996) also found that blinded raters scored reports significantly ($p < 0.001$ and $p < 0.01$) lower when using the 6- and 3- item scale, respectively, compared with open raters. Jadad et al. (1996) explained that the consequence of this is "non-randomised trials or randomised controlled trials that do not use a double-blind design are more likely to show advantage of an innovation over a standard treatment".

The Jadad 3-item instrument was the final version selected by Jadad et al. (1996) for quality assessment. The 3-item scale concentrates on the report into the control of bias in the study alone, which the authors explain allows the scale to be used in a variety of situations, not just in research to pain relief. The 3-item scale also yielded similar scores to the 11- and 6-item scales, but with greater inter-rater reliability. Although blinding significantly reduced the mean scores allocated by the raters, this may not be feasible for independent researchers. Jadad et al. (1996) provide guidance notes on the use of the Jadad 3-item scale and allocation of points to reports (Appendix C). The Jadad 3-item scale has been adopted in this review as a means of assessing the control of bias, an aspect essential in any clinical trial.

Use of the Jadad 3-item scale to measure the likelihood of bias in clinical trials requires the researcher to respond to the following three questions relating to the study in question.

1. Was the study described as randomised?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

These questions highlight key aspects directly related to bias reduction. For each question which can be answered with a “yes” for the study concerned one point can be allocated. Randomisation in the case of clinical trials refers to the random sampling of a population or the uncontrolled distribution of subjects to treatment groups (drug or placebo). In terms of the Jadad 3-item scale, this entails the use of words such as random, randomly or randomisation when describing the sampling process. An additional point may be awarded if the method to generate the sequence of randomisation was described and was considered appropriate (e.g. table of random numbers, computer generated, etc.). If the process of randomisation described is inappropriate (patients allocated alternately, date of birth or submission, etc.) one point should be deducted from the score.

Question two, double blinding, refers to the method by which neither the investigator nor the study participants are able to identify the intervention being assessed. Double blinding is a strong factor in controlling bias as indicated by Jadad et al. (1996). A point may be awarded if the use of the term

“double blind” is used. An additional point may be awarded if the process of double blinding is described and was considered appropriate. Examples provided by Jadad et al. (1996) include use of identical placebo, active placebo or dummies. A point may be deducted if the process described is inappropriate and the examples provided include, for example, comparison of tablet vs. injection with no double dummy.

The final point available regards adequate description and explanation of any withdrawals or dropouts of participants from the study. The authors are required to provide the number and reasons for withdrawal in each group to be awarded the point. Studies which indicate the number of subject withdrawals, but fail to provide an adequate explanation cannot be awarded the point. Explanation of subject withdrawals are important as, if the reasons are related directly to the intervention (e.g. undesirable side-effect), it is imperative that these details are considered in the final analysis. Therefore the maximum number of points a single study can receive for comprehensive reporting of controlling of bias is five points. The least a single study can receive is zero, for reporting on no factors related to the control of bias.

A worked example to demonstrate the application of the quality assessment related directly to the control of bias is present in Table 2.

Table 2 – Demonstration of Jadad et al. (1996) 3-item Quality Assessment of Studies on Chromium Supplementation and Physical Performance in Controlling Factors of Bias.

Principal Author	Date	Jadad 3-item Quality Assessment Scale					
		Randomisation		*Double Blinding*		*Withdrawals*	**Total Score (out of 5)**
		Yes/No	Method Described & Appropriate?	Yes/No	Appropriate?	Statement	
Davis	2000	0	0	1	1	0	2/5
Walker	1998	1	1	1	1	0	4/5

The two studies selected for the purposes of demonstrating the quality assessment process of the Jadad 3-item scale is a study by Davis, Welsh and Alderson (2000) into the effects of short-term, acute ingestion of chromium ingestion during intermittent high-intensity exercise to fatigue and a study by Walker, Bemben, Bemben and Knehans (1998) into the effects of long-term ingestion of chromium on body composition and muscular performance (both to be reviewed in full during 6.0 Results section). The quality assessment process demonstrated a wide difference in control for bias by the two studies. Davis et al. (2000) mentioned that the administration of the placebo and chromium to the subjects was double-blind, and the method of blinding was appropriate. As the study design by Davis et al. (2000) was repeated measures there was no requirement for random administration of subjects to treatment or placebo groups. However, Davis et al. (2000) failed to indicate whether the order in which participants received the treatment (carbohydrate plus chromium, carbohydrate only or placebo beverage) was randomised. Eight subjects participated in the Davis et al. (2000) study, but there is no statement of withdrawals or dropouts, therefore, using the guidelines set out by Jadad et al. (1996), no points can be allocated. The study by Davis et al.

(2000) received a total of two points out of a maximum of five for reporting the control of bias.

Walker et al. (1998) provide a thorough report into the control of bias within their study, receiving four out of a maximum of five points for control of bias. These points were allocated because the authors adequately explained that the process by which subjects were randomly assigned to either a chromium, placebo or control group, was by stratified random sampling. Walker et al. (1998) also described that the study was conducted in a double-blind fashion, and the placebo received was sodium diphosphate, similar in appearance to the chromium capsules. The authors did not describe compliance or withdrawals of subjects from the study, which prevented allocation of the maximum points for the reporting of the control of bias.