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Mr. Orgah Adikwu Emmanuel
INTRODUCTION

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a VMP to Competent Authorities at defined time points post-authorisation. At these times, MAHs are expected to provide succinct summary information on all adverse events together with a critical evaluation of the benefit-risk balance of the VMP in the light of any new or changing pharmacovigilance information.

This evaluation is necessary to ascertain whether further investigations need to be carried out and/or whether changes should be made to the SPC or other product information.

For VMPs:

- purely nationally authorized;
- authorized within the scope of Directive 87/22/EEC (ex-concentration procedure);
- that have benefited from the MRP or the DCP in accordance with Directive 2001/82/EC;
- that have been subject to referrals considered under Articles 36, 37 and 38 of Directive 2001/82/EC,

PSURs should be submitted to DGV in accordance with point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October.

The requirement for the submission of a PSUR applies irrespective of whether the VMP is marketed or not.

KEYWORDS

PSUR, Investigation, Report, Safety Signal, Events, DGV
ARTICLE SUMMARY

A PSUR is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorization. At these times, marketing authorization (MA) holders are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information.

This evaluation should ascertain whether further investigations need to be carried out and whether changing information. This evaluation should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorization and product information. PSURs must be submitted for all registered products regardless of marketing status. A single report may cover all products containing the same active substance(s) licensed by one MA holder.

The report will usually include all dosage forms and formulations, as well as all indications, associated with such an active. Within the PSUR, separate presentations of data for different dosage forms, indications or populations (for example, children vs. adults) may be appropriate, however an overview of the combined data should also be provided. For combinations of substances which are also registered individually, safety information for the fixed combination may be reported either in a separate PSUR or be included as a separate presentation in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is essential.

ARTICLE STRUCTURE

The periodic safety update report for marketed drugs (PSUR) was designed to be a stand-alone document that allows a periodic but comprehensive assessment of the worldwide safety data of a marketed drug or biological product. The PSUR can be an important source for the identification of new safety signals, a means of determining changes in the benefit-risk profile, an effective means of risk communication to regulatory authorities and an indicator for the need for risk management initiatives, as well as a tracking mechanism monitoring the effectiveness of such initiatives. For these reasons, the PSUR can be an important pharmacovigilance tool.

Numerous steps are involved in the PSUR process including: intake of adverse drug reaction information, case processing, data retrieval, data analysis, and medical review and risk assessment. These processes are heavily reliant on the availability of adequate resources. An overarching principle throughout the PSUR process is the need for a proactive approach in order to identify the critical steps in the process and to have a clear understanding of the consequences of any critical 'mis-step'.

With this information comes appropriate planning, building quality into each step of the PSUR process and monitoring performance will maximize the likelihood of generating a quality report. Any failure of a key PSUR process will have the opposite effect - a poor quality report that will give little insight into emerging safety signals or provide misleading information that can adversely affect public health.
pragmatic approach that will avoid or minimize these pitfalls includes the following: adequate resource planning, training, development of 'scripts' designed to maximize the capture of key information for medically important reactions, standardized and harmonized Medical Dictionary for Regulatory Activities (MedDRA) coding procedures, pre-specified search criteria for data retrieval, ongoing medical review, and metrics to evaluate the effectiveness and efficiencies of these processes. With these quality measures in place, the utility of the PSUR as an effective pharmacovigilance tool is enhanced.

GENERAL PRINCIPLES

GENERAL SCOPE OF INFORMATION

MAHs must include in the PSURs of all VMPs, details of all adverse events arising in the EEA and in a third country. The main focus of the PSUR should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR, providing a basis for conclusion whether further investigations or changes in the SPC will be necessary. For this purpose the PSUR should include information on the following types of adverse event reports/case histories received during the period of review:

- All adverse events in animals and in human beings, sent spontaneously to the MAH and occurring in the EEA and in a third country, including information from literature.
- All adverse events forwarded to the MAH by an NCA;
- Any suspected transmission of an infectious agent via a VMP;
- Serious and nonserious adverse event reports from post-authorization safety studies;
- Any available information on investigation of the validity of a withdrawal period or any potential environmental problems, caused by the product under the normal conditions of use;
- Any available information on investigation of adverse events related to off-label use;
- Any available information on lack of expected efficacy, as specifically for VMPs used in the treatment of life-threatening conditions and for certain other VMPs, e.g. antibiotics or vaccines, lack of expected efficacy may represent a significant hazard and in that sense may give rise to a safety concern;
- Any data from previously requested close monitoring.
FREQUENCY AND TIMING OF PERIODIC SAFETY UPDATE REPORTS

SUBMISSION OF PSURS

The periodicity for submission of PSURs is established in point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October. Unless other requirements have been laid down as a condition of the granting of the MA, a PSUR should be prepared immediately upon request or at least every six months after authorization until the placing on the market. Following the initial placing on the market, PSURs shall be submitted immediately upon request, or at the following intervals:

- 6-monthly for the first 2 years
- Annually for the subsequent 2 years, and
- Thereafter, at three-yearly intervals.

For products authorized through the MRP or DCP, the PSUR submission schedule should be agreed on and be the same for all involved NCAs. The PSUR cycle should be based on the EU Birth Date (EBD, date of the first marketing authorization within the European Union) of a VMP or its International Birth Date (IBD, date of the first marketing authorization for the product granted to the MAH in any country in the world), or the EU HBD (EU Harmonized Birth Date for VMPs included in the work sharing initiative on PSUR assessments, provided it is not against National Legislation).

Once a VMP is authorized in the EU, even if it is not marketed, the MAH is required to submit PSURs at 6-monthly intervals, until initial placing of the VMP on the market. When launch dates are planned, this information should be reflected in the forthcoming PSUR. The PSUR covering this period during which the product is launched is considered the last of the six-month PSURs to be submitted before ‘initial placing on the EEA market’.

After this initial placing of the product on the EEA market, the MAH should submit at least four PSURs covering 6 months each, in order to ensure that two full years of experience with the product on the EEA market are covered through provision of 6-monthly PSURs, while keeping the DLP according to the EBD, EU HBD or IBD.

PSUR REPORTING PERIOD

Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the DLP. Gaps are not allowed. Overlapping should be avoided. DLPs should be set according to the EU Birth Date (EBD, date of the first marketing authorization within the European Union) of a VMP or its International Birth Date (IBD, date of the first marketing authorization for the
product granted to the MAH in any country in the world), or the EU HBD (EU Harmonized Birth Date for VMPs included in the work sharing initiative on PSUR assessments).

**PREPARATION OF PSURS ACCORDING TO THE INTERNATIONAL BIRTH DATE**

VMPs, which are also authorized outside the EU, will have an IBD. This is the date of the first marketing authorization for the product granted to the MAH in any country in the world. For VMPs first authorized in the EU, the EBD is the IBD. For administrative convenience, if desired by the MAH, the IBD may be designated as the last day of the same month.

In order to harmonize PSURs internationally, the MAH may use the IBD to determine the DLPs in the EEA rather than the EBD. If the IBD is used, the first DLP must be within 6 months of the EBD, unless other requirements have been laid down at the time of granting the MA. Regardless of whether the IBD or EBD is used, the PSUR should be submitted within the 60 days following the DLP, taking into account that the date of submission of the PSUR is in compliance with the stipulated submission schedule.

For purely nationally authorized VMPs that are marketed, the MAH may wish to synchronize national birth dates with the IBD. Such a step may be feasible and should be discussed with DGV. For nationally authorized VMPs, including those authorized through the MRP or DCP, where national birth dates are used to determine the submissions of PSURs, the MAHs and NCAs voluntarily may agree on an EU HBD which may be the IBD.

Thus the first PSUR to be submitted in the EU should be based on the EU HBD and should cover a period in accordance with the life cycle of the VMP in the EU (6 months, 1 year or 3 years). When PSURs have previously been submitted in MS based on different national birth dates, DGV accept that there may be an overlap between the last PSUR based on a national birth date and the first PSUR based on the EU HBD.

**CONTENT OF PERIODIC SAFETY UPDATE REPORTS – MARKETED PRODUCTS**

For marketed VMPs, the PSUR should fulfil the following format and content: MAH and product details. Each PSUR should include:

i) The VMP name(s)

ii) The name of the MAH

iii) The MA number(s)
iv) Procedure number, if applicable

v) EBD / Start date for PSUR-submission cycle

vi) The period covered by the PSUR

vii) The date of initial placing of the product on the EEA market, understood as the date when the first presentation of the product was first placed on the market in any MS.

viii) Chronological order of PSUR (e.g. 1st 6 month PSUR after initial placing on the market)

**UPDATE ON REGULATORY OR MAH ACTIONS TAKEN FOR SAFETY REASONS**

An overview of regulatory and MAH actions taken for safety reasons (e.g. follow-up measures, specific obligations and variations) since the last period covered in the PSUR indicating scope, status and date should be given. Significant changes in the wording of the SPC should be explained, where of relevance to safety.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The latest version of the relevant SPC must be included for reference in the report. It is recommended that when the SPC changed significantly in matters relevant to safety during the covered period, the nature of the change(s) should be succinctly explained in the PSUR. If evaluation of safety data leads to any proposed changes in the SPC, these should be described, see Part I Section 3.1.9.

- For VMPs authorized through MRP or DCP, this will be the mutually accepted SPC in English.

- For nationally authorized VMPs, the specific national SPC in Portuguese language should be included.

If no SPC is available, e.g. in cases of old non-reviewed/renewed VMPs, an explanation should be given and the package leaflet should be provided. It is preferable that the SPC(s) are included in an annex.

**ESTIMATIONS OF EXPOSURE**

*SALES VOLUME*
Each PSUR should contain the number of doses/amount of VMP sold within the reporting period in the relevant Member State(s) and third countries, if applicable. The sales information should be expressed per presentation in an appropriate form. The following forms are suggested:

- Vaccines- to be expressed in numbers of doses;
- Liquid- to be expressed in litres;
- Powder- to be expressed in kilograms;
- Tablets- to be expressed in numbers of tablets;
- Sprays- to be expressed in litres or kilograms;
- Flea collars- to be expressed in numbers of collars;
- Paste- to be expressed in kilograms
- Pipettes for spot-on solution - to be expressed in numbers of pipettes.

**INCIDENCE OF ADVERSE EVENTS**

A PSUR must address the relationship between the sales volume of a VMP and the numbers of adverse events reported. An overall incidence should be calculated for all spontaneous adverse reactions (A, B, O, including O1) that occur after recommended or non-recommended (off-label) use in the target species. For clarity, adverse reactions from post-authorization safety studies should be excluded. In this respect the use of a VMP in non-authorized species under specific conditions laid down in Article 78.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, is regarded as off-label use. In addition, an incidence for lack of efficacy in target species after recommended use should be calculated, when relevant.

When a VMPs is indicated for more than one target animal species, it is suggested that in addition to the ratio of all animals expressing an event the ratio be computed for each species based on the estimated conditions of use of the VMP (sales/species) (see 3.1.4). This information is of importance to NCAs although the arbitrary nature of such calculation based on assumptions is recognized. For the calculation of incidence of adverse reactions it is suggested that MAHs adopt the following two-tier approach:
CALCULATION 1 – RATIO OF ANIMALS EXPRESSING AN ADVERSE EVENT

In the first instance, the ratio of the number of animals expressing an adverse event (reports assigned a causality code of A, B, O, including O1, N) during a period to the amount of VMP sold during that period should be computed:

No of animals with adverse event during period

Ratio of animals with adverse event = No of doses sold during the period

This calculation is based on data that tends to be accurate and can be used reliably to monitor trends from one PSUR to the next. Any increase in this ratio relative to previous PSURs may signal a problem and the need for more detailed evaluation of the pharmacovigilance data.

CALCULATION 2 – INCIDENCE

The incidence (%) of adverse reactions (reports of adverse events assigned a causality code of A, B or O, including O1) should be calculated by dividing the total number of animals reacting during the period by an estimate of the number of animals treated during the period of the report and multiplying by 100.

No of animals reacting during period (coded A, B or O and O1) x 100 % Incidence = Estimated No of animals treated during the period

For VMPs authorized in multiple MS, incidence should be calculated individually for each MS where sales have occurred. This calculation may then be revised to exclude O and O1 coded reports (that is, this calculation would focus on A-probable - and B-possible - coded reports only).

The values included in the calculation of incidence must be justified.

It is expected that the values used for estimation of the number of animals treated would be representative of the conditions of use of the VMP. All assumptions used for calculation should explicitly be stated. Overall incidences are calculated for the EEA in total, regardless of the route of authorization of the VMP.

DATA REVIEW

The report should include a data review based on the MAHs analysis (including causality assessment) of the individual adverse events reported during the period concerned by the PSUR. The analysis of the adverse events reported should be supported by tables or tabulations summarizing the main findings. It may be helpful, especially for PSURs which contain a large number of adverse events, to introduce summary tabulations and prepare separate tables e.g. for serious expected reactions, serious unexpected
reactions, non-serious unlisted reactions (not mentioned in the SPC), or on basis of VEDDRA categories on organ level (e.g. System Organ Class (SOC) or Preferred Term (PT) level).

The data review should be structured as follows:

- Adverse events in target species, including events of lack of efficacy and those events occurring after off-label use in target species;
- Adverse events reported in humans;
- Other pharmacovigilance fields:
  - Adverse events after use in non-target species;
  - Investigations of the validity of the withdrawal period;
  - Transmission of any infectious agent via a veterinary medicinal product;
- Potential environmental problems arising from the use of the VMP.

**NON-SPONTANEOUS REPORTS**

A narrative overview of available data from other sources (e.g. post-authorisation safety studies, published adverse event reports, user experience studies) should be included in this section. The data should be analysed and discussed as part of the benefit-risk assessment. The overview should include a review of all adverse event reports eligible for expedited reporting that were received during the PSUR period from post-authorisation safety studies. Summaries from post-authorisation safety studies should be included once final results become available, and should consider all adverse events reported from the study.

**OBJECTIVITY:**

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of authorisation status information for initial and renewal applications, and data on serious, unlisted adverse reactions. These should be provided for both the period in question and as cumulative summary tabulations starting from the International Birth Date (IBD).

The main focus of the report should be adverse reactions. Unless indicated otherwise by the reporting health-care professional, all adverse experiences reported spontaneously should be considered adverse reactions; for clinical study and literature cases, only those judged not related to the medicinal product by both the reporter and the MA holder should be excluded. The PSUR should include a scientific evaluation of the risk: benefit balance of the product(s), and should be generated according to the ICH E2C guidelines.
CONCLUSION

Any failure of a key PSUR process will have the opposite effect - a poor quality report that will give little insight into emerging safety signals or provide misleading information that can adversely affect public health. A pragmatic approach that will avoid or minimise these pitfalls includes the following: adequate resource planning, training, development of 'scripts' designed to maximize the capture of key information for medically important reactions, standardized and harmonized Medical Dictionary for Regulatory Activities (MedDRA) coding procedures, pre-specified search criteria for data retrieval, ongoing medical review, and metrics to evaluate the effectiveness and efficiencies of these processes. With these quality measures in place, the utility of the PSUR as an effective pharmacovigilance tool is enhanced.

REFERENCES


PERSONALIZED MEDICINE, PHARMACOGENOMICS AND PHARMACOVIGILANCE

A Case Study By Dr Deven V Parmar\textsuperscript{1} & Dr. Dharani Munirathinam\textsuperscript{2}, USA

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INTRODUCTION

Personalized medicine is the ability to determine an individual's unique molecular characteristics and to use those genetic distinctions to diagnose more finely an individual's disease, select treatments that increase the chances of a successful outcome and reduce possible adverse reactions.

Personalized medicine also is the ability to predict an individual's susceptibility to diseases and thus to try to shape steps that may help avoid or reduce the extent to which an individual will experience a disease. The essentials of personalized medicine are an electronic medical record, personalized genomic data available for clinical use, physician access to electronic decision support tools, a personalized health plan, personalized treatments, and personal clinical information available for research use.

An important aspect of personalized medicine is to identify patients with possible problematic adverse events before administration of a drug and their avoidance. This is on the one hand of great benefit for the patient. On the other hand it also helps to avoid hospital admissions due to severe adverse events.

This is possible through pharmacogenomics. Pharmacogenomics utilizes a patient's genetic information to identify genetic variants that have the potential to provide clinically relevant predictions of toxicity and efficacy. The goal is to develop personalized and genetic-based predictions of an individual's drug response and likelihood of experiencing an adverse drug reaction, because Adverse drug reactions (ADRs) rank as one of the top 10 leading causes of death in the developed world, and the direct medical costs of ADRs exceed $100 billion annually in the United States alone. Recent evidence suggests that many ADRs are the result of genetic factors. The emerging field of pharmacogenomics aims to identify genetic variations that are associated with drug toxicity in order to optimize patient therapy [1].
KEYWORDS

Personalized medicine, Drug, Age, Environmental Factor, Trials, Prescription

PHARMACOGENOMICS AND DRUG SAFETY

The safety and efficacy of a drug is evaluated according to strict regulatory guidelines, however substantial variation exists among individuals. This could be due to genetic and environmental factors. The environmental factors include age, disease, and diet and drug interactions. The genetic composition of every individual is unique, resulting in individual variation. The traditional approaches to drug development such as trial and error, one drug and dose for all are very limited and contribute for 20-50% of drug toxicities or treatment failures.

Genetics provides significant opportunities to maximize the safety and efficacy of drugs. The field of pharmacogenomics began with a focus on drug metabolism, but it has been extended to encompass the full spectrum of drug disposition, including a growing list of transporters that influence drug absorption, distribution, and excretion [2].

POTENTIAL APPLICATIONS OF PHARMACOGENETICS (PGX)

Option 1: using PGx to discover better drugs discovering drugs for specific genomic sub-groups (allelic variants of drug target). Discovering drugs that work in all sub-groups (ensuring leads work in all allelic variants).

Option 2: PGx to improve the safety of new drugs in development early stage trial design and/or monitoring (for example, ensuring balanced trial population of cytochrome P450 variants). ‘Rescue’ of drugs that fail clinical trials owing to safety problems.

Option 3: PGx to improve the efficacy of new drugs in development Targeting late-stage trials as ‘good responders’ (prospective). ‘Rescue’ of drugs that fail clinical trials owing to lack of efficacy (retrospective).

Option 4: improving the safety of licensed drugs Pre-prescription patient testing for risk of adverse drug reactions (ADRs) (for example, thiopurinemethyltransferase). Label and market extension of drugs that have been restricted by ADRs (for example, abacavir). Improved post-marketing surveillance.

Option 5: improving the efficacy of licensed drugs Pre-prescription patient testing to identify good responders. The use of efficacy data in drug marketing.
Collaborative links and strategic options for the use of PGx commercially from the early stage of lead discovery (1) to its use when health care is being provided to patients (5). Dotted arrows in the figure indicate points of intervention in the drug development trial process [3].

![Diagram of drug development process](image)

**CANDIDATE GENE**

Candidate gene studies have been at the forefront of genetic association studies i.e. identifying risk variants associated with a particular disease. Candidate gene studies are relatively cheap and quick to perform, and are focused on the selection of genes that have been in some way related to the disease previously and thus come with prior knowledge about gene function.

Each candidate gene and polymorphism (gene variant) must be studied individually, to identify associations with response. Despite such limitations, this approach has given clear evidence for the rationale of pharmacogenetics. Polymorphisms in drug metabolizing enzymes have been shown to impact on the rate of metabolism of many drugs. This can have an impact on treatment outcome and, in the case of a decreased rate of metabolism for some drugs, an increased risk of adverse drug reactions (ADRs).

In addition to the genetic control of metabolism there is also increasing evidence linking gene variants involved in a drug's mode of action with clinical response. In asthma patients, for example, recent data suggests that poly-morphisms in the 5-lipoxygenase gene (ALOX5) and the LTC4 synthase gene which are both associated with the synthesis of leukotrienes can negatively impact the therapeutic response to leukotriene antagonists. A second example is that seen with the cholesterol lowering agent, pravastatin. Here data suggests that those patients who are homozygous B 1 for the cholesterol ester transfer protein (CETP) gene gain greatest benefit as measured by a delay in progression of coronary
atherosclerosis. Using this type of information it may be possible to develop gene-specific profiles that can be used to determine which patients will benefit from a given medicine [4].

GENOME-WIDE ASSOCIATION STUDIES

A genome-wide association study (GWA study, or GWAS), also known as whole genome association study, is an examination of many common genetic variants in different individuals to see if any variant is associated with a trait. GWAS typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major diseases. The ability to accurately predict patient response will inevitably change the way medicines are developed, evaluated, and prescribed. Advances in single nucleotide polymorphism (SNP) map technology are likely to drive this innovation.

Abbreviated SNP profiles will provide the means to define medicine response tests, thereby allowing clinicians to select the medicine to which the patient is likely to gain the greatest benefit and least risk. This will help to maximize efficacy and reduce the incidence of drug-related adverse events. In addition it may be possible to incorporate pharmacogenetics into post marketing surveillance strategies to provide a means to identify SNPs which predict uncommon serious adverse drug reactions, and so refine the initial medicine response test.

The ability to develop drugs with a predictable response will allow clinicians to provide targeted treatment for patients, with greater confidence of safety and efficacy. Patients therefore will receive more efficacious, timely, and well-tolerated medicines [4].

The SNP map technology is a major advance in genetic research has been provided by a proof of principle study which used SNP mapping to locate the APOE Alzheimer disease susceptibility gene on chromosome. This susceptibility gene had previously been identified using traditional methods. A high-density SNP map for a 4-million base region around APOE was constructed. Using DNA from Alzheimer disease and control subjects it was possible to identify SNPs in linkage disequilibrium (LD) and associated with Alzheimer disease. Only two genes APOCI and APOE are coded in the physical DNA segment defined by the SNPs associated with Alzheimer disease.

The advantage of this technique is that it does not rely on making an assumptions regarding disease-susceptibility genes. As a result it is possible to more accurately and recently narrow down gene selection. SNP technology has now been used to narrow successfully the search for susceptibility genes in areas of linkage for several other diseases. These include migraine with aura, psoriasis and type-2 diabetes mellitus. As for these disease phenotypes, it is anticipated that it will be possible to identify SNPs in LD that are associated with medicine related phenotypes [4]. Genetic variation in drug targets (e.g., receptors) can have a profound effect on drug efficacy, with few examples identified (Table 1) [2].
NEXT-GENERATION SEQUENCING

In recent years, pharmacogenomics has moved beyond candidate gene and genome-wide association studies towards truly personalized genomics. The use of new biotechnological, mathematical and computational tools has enabled an exponential increase in the number of biomarkers for drug safety and efficacy.

The development of next-generation sequencing (NGS) technology has led to a drastic drop in the cost (>10,000-fold) and time (from 10 years to 1 week) needed to sequence a genome. NGS is now being introduced as a method to personalize medicine.

The concept behind NGS technology is similar to CE- the bases of a small fragment of DNA are sequentially identified from signals emitted as each fragment is re-synthesized from a DNA template strand. NGS extends this process across millions of reactions in a massively parallel fashion, rather than being limited to a single or a few DNA fragments. This advance enables rapid sequencing of large stretches of DNA base pairs spanning entire genomes, with the latest instruments capable of producing hundreds of giga bases of data in a single sequencing run [5].

### Table 1. Genetic Polymorphisms in Drug Target Genes That Can Influence Drug Response.

<table>
<thead>
<tr>
<th>Gene or Gene Product</th>
<th>Medication</th>
<th>Drug Effect Associated with Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>ACE inhibitors (e.g., enalapril)</td>
<td>Renoprotective effects, blood-pressure reduction, reduction in left ventricular mass, endothelial function</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin</td>
<td>Lipid changes (e.g., reductions in low-density lipoprotein cholesterol and apolipoprotein B); progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or regression of coronary atherosclerosis</td>
</tr>
<tr>
<td>Arachidonate 5-lipoxygenase</td>
<td>Leukotriene inhibitors</td>
<td>Improvement in FEV1</td>
</tr>
<tr>
<td>β2-Adrenergic receptor</td>
<td>β2-Agonists (e.g., albuterol)</td>
<td>Bronchodilatation, susceptibility to agonist-induced desensitization, cardiovascular effects</td>
</tr>
<tr>
<td>Bradykinin B2 receptor</td>
<td>ACE inhibitors</td>
<td>ACE-inhibitor–induced cough</td>
</tr>
<tr>
<td>Dopamine receptors (D2, D3, D4)</td>
<td>Antipsychotics (e.g. haloperidol, clozapine)</td>
<td>Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinesia (D3),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>antipsychotic-induced acute akathisia (D3)</td>
</tr>
<tr>
<td>Estrogen receptor-α</td>
<td>Conjugated estrogens, Hormone-replacement therapy</td>
<td>Increase in bone mineral density</td>
</tr>
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<td></td>
<td></td>
<td>Increase in high-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>Glycoprotein Illa subunit of glycoprotein IIIa</td>
<td>Aspirin or glycoprotein tib/Il/IIIa inhibitors</td>
<td>Antiplatelet effect</td>
</tr>
<tr>
<td>Serotonin (5-hydroxytryptamine) transporter</td>
<td>Antidepressants (e.g., clomipramine, fluoxetine, paroxetine)</td>
<td>5-Hydroxytryptamine neurotransmission, antidepressant response</td>
</tr>
</tbody>
</table>

* The examples shown are illustrative and not representative of all published studies, which exceed the scope of this review. ACE denotes angiotensin-converting enzyme, and FEV1 forced expiratory volume in one second.
TARGETED SEQUENCING SAMPLE PREP AT A GLANCE

CE-BASED SANGER SEQUENCING NEXT--GENERATION SEQUENCING

<table>
<thead>
<tr>
<th>Library preparation more involved- each sample must contain a single template, either from a single PCR purified from single bacterial colonies</th>
<th>Library preparation more streamlined- each sample can be a population and does not require clonal purification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitable for sequencing amplicons and clone checking</td>
<td>Suitable for sequencing amplicons and clone checking</td>
</tr>
<tr>
<td>Complete within days to weeks, depending upon the size of the genome being sequenced</td>
<td>Complete within hours</td>
</tr>
</tbody>
</table>

PERSONALIZED MEDICINE AND PHARMACOGENOMICS

Personalized medicine is the use of new methods of molecular analysis to better manage a patient’s disease or predisposition toward a disease. It aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best in the context of the patient’s unique genetic and environmental profile.

Personalized medicine promises many medical innovations, and has the potential to change the way treatments are discovered and used. Personalized medicine stands poised to transform healthcare over the next several decades. New diagnostic and prognostic tools will increase our ability to predict the likely outcomes of drug therapy, while the expanded use of “biomarkers” – biological molecules that are associated with a particular disease state – could result in more focused and targeted drug development. Personalized medicine also offers the possibility of improved health outcomes and has the potential to make healthcare more cost-effective.
The Paradigm of personalized medicine can be illustrated as follows [6].

This arrow reflects the current and anticipated flow of healthcare services, and changing points of intervention, as medicine becomes more personalized. Early detection testing will continue based on large population risk (e.g., mammograms), while new forms of risk assessment will be incorporated (e.g., determining which women carry the genetic variation that increases their risk for developing cancer). Though true prevention must occur before disease symptoms are present, better risk assessment enables more targeted monitoring (e.g., women with the genetic variation should have more frequent mammograms); followed by symptom-driven diagnosis, in which molecular monitoring could possibly identify disease subtypes that cannot be clinically determined. Such diagnosis may or may not lead to targeted therapy, but in either event we may also benefit from improvements in monitoring a patient’s response to a particular therapy [6].

The factors that affect the adoption of PGx through case studies of Clozapine (Clozaril; Novartis), as this drug was chosen because it is known to produce different responses depending on genotype and require monitoring regimes to ensure patient safety. We found that, in general, improved practices in prescribing drugs or patient experience (by getting the right dose earlier and avoiding ADRs), and the chance to refocus health service costs (by avoiding wasteful treatment), were the important factors behind the introduction of PGx in these cases.

However, there were concerns about the use and practicality of PGx in specific clinical contexts and about the weakness of the current evidence on which support for its introduction was based. To illustrate these points, we will make some brief suggestions on the basis of our analysis of clozapine, which is used as an antipsychotic drug for patients with schizophrenia who do not respond to, or cannot tolerate, other drugs.

Clozapine is effective in up to 50% of patients who do not respond to other drugs and 80% of those who suffer from intolerable side effects from other drugs. However, the drug itself is associated with potentially fatal blood disorders (notably AGRANULOCYTOSIS), which necessitates a laborious and time-consuming blood monitoring process. PGx testing could, in principle, be used to identify not only those who suffer this response, but also those who are likely to be ‘good responders’. By prescribing the drug only to patients who do not suffer agranulocytosis and who meet the second criteria, the overall level of ADRs could be reduced [3].

Clinicians currently have little evidence of the utility, or even the validity, of PGx in clinical contexts. Assuming that validity (analytical and clinical) can be proven, utility remains a conspicuous hurdle;
this is where visions of PGx meet the reality of existing clinical practice. Generic criteria that have been suggested for judging the clinical use of PGx tests have included the value that is added to treatment objectives (such as prompt therapeutic response), the existence of other treatments, the size of the patient population and the scale of negative effects that might be avoided. It has also been recommended that PGx tests are verified, with reference to reliability, information provided, and the frequency and magnitude of the response that it predicts. However, in routine clinical decision making, information about drug response can be just one of the many influencing factors [3].

To encourage clinical adoption, it will be imperative for health practitioners to be in possession of clear information that links genotypes to clinical outcomes, and to have specific advice on how this might affect prescribing decisions, or alter drug dosage. PGx might require a culture shift in prescribing practice and might generate a need for (re-) education of health professionals. Finally, there might be ethical concerns associated with denying treatment as a result of a person being assigned into a particular category of genotype.

For example, patients might be excluded from using a particular drug as a result of a PGx test that indicated that they are ‘at risk’ from ADR, when evidence for this might only be probabilistic; it has been argued that clinical decision-making in regard to drug therapy should not solely be on the basis of gene association, but on a detailed patient history. The gradual use of PGx testing in the context of oncology, for example, reflects both the scale and importance of this disease area. It also demonstrates the need to improve the therapeutic value of existing drugs: results from studies on gene expression profiling in the cancer field to predict drug response illustrates how PGx testing might begin to meet the twin demands of use and practicality [3].

Numerous pharmacogenetic biomarkers for drug safety and efficacy have been identified over the past few years. At the 9th Annual Cold Spring Harbor/Wellcome Trust meeting ‘Pharmacogenomics and Personalized Medicine’, biomarkers relating to a wide range of drugs were presented: from anticoagulants to immunotherapy, chemotherapy, antiretroviral therapy, antiepileptic drugs and antibiotics.

The US Food and Drug Administration have currently more than 70 black box warnings for these drug-gene interactions. The European Medicines Agency has been considerably more conservative in this respect. The fact that only a few pharmacogenetic biomarkers have reached the clinic was touched upon by several speakers, most notably Muin J Koury (Office of Public Health Genomics, USA).

Koury defined the translation process from genomic research to clinical and public health interventions as a cycle of five phases: T0 to T4 (in the below figure). Although the first phase of translation has acceptable levels of funding, subsequent phases are comparatively under-resourced and lack the necessary infrastructure; thus, priority should be given to these areas of research. After his presentation, the question of whether genetic biomarkers for drug response need the same level of evaluation as biomarkers for disease risk was raised.

This discussion was continued when for the first time in the Cold Spring Harbor Laboratory/Wellcome Trust series of pharmacogenomics meetings, a debate took place. It was led by Hiltrud Brauch (Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Germany) and Paul Pharoah (Cambridge Cancer Centre, UK). The question set was: does \textit{CYP2D6} genotyping for response to tamoxifen
treatment of estrogen-positive breast cancer have clinical validity and utility? Brauch presented arguments for, and Pharoah against, genotyping of CYP2D6. The issue was not settled here, but it initiated a heated discussion that was very well received by the contributing audience. In reality, the uptake of this and many other pharmacogenetic tests into the clinic has been slow because of the lack of evidence for clinical validity and utility. Concentrated efforts should be made to provide this evidence before pharmacogenetic tests are translated on a broad scale into clinical recommendations and policies [7].

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THE GENOMICS TRANSLATION (T) HIGHWAY

This model describes the translation from bench to bedside, and the knowledge that is synthesized from all parts of the process: T0, public health drives discovery; T1, discovery to application; T2, application to guideline; T3, guideline to practice; and T4, practice to population health impact. [7]

Despite current reluctance to adopt pharmacogenetic testing, Leroy Hood (Institute of Systems Biology, USA) predicts that in 10 years time each patient will be surrounded by billions of data points: DNA sequence, imaging and test results, and so on. However, most of these data points will be biological noise, and how to select the relevant data, integrate them and formulate them into models will be the key to the future.

The challenge will be to deal with this incredible complexity to decipher biological pathways implicated in disease and response to drugs. Hood described how emerging biotechnological, computational and mathematical tools will enable medicine to focus more on health (wellness) than disease. He calls the transition from reactive to proactive medicine P4 medicine, which is the term
coined for predictive, preventive, personalized and participatory medicine. This is clearly an area of research for the future [7].

**CONCLUSION**

Personalized medicine focuses on individualized drug treatment according to each patient’s molecular diagnosis and genetic makeup and involves optimal drug selection and dose adjustment. Drug safety is the priority, since patients can benefit from Pharmacogenetics. Pharmacogenetic technology offers significant opportunities to improve the discovery, development and delivery of medicines. Pharmacogenomic research is about to take the plunge into NGS. This technology, together with international collaborations to achieve large sample sizes, will surely be fruitful for pharmacogenetic research. Many biomarkers for drug safety and efficacy have been detected already, and we expect the number to increase over the next few years. The translation of pharmacogenomic biomarkers into the clinic will therefore be a greater endeavor than their discovery.

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PATIENT SAFETY: A FUNDAMENTAL ASPECT OF CLINICAL TRIALS THROUGH A REVIEW OF A STUDY ON CANADIAN ADVERSE EVENTS

A Case Study By Pramod Kumar Jagannathrao Wable, UK
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Email: pjwable@gmail.com

SOURCE:


ABSTRACT

Patient safety has received growing attention worldwide sin last decade or two in clinical research. Identification and immediate reporting of an Adverse Event (AE) has always been one of the key parameters to assess and observer patient’s safety in clinical research. Compromise to the patient safety was evident as critical violation of the International Harmonization Conference (ICH) - Good Clinical Practice (GCP) requirements of clinical research.

This review was written after comprehensive and critical assessment of the research conducted by G. Ross Baker et.al. This review provided a synthesis of key principles of identification of AEs and determination of their preventability. It examined detail article structure considering the sample size, research population and relevance to the research topic. The review further critiqued on the article authority and creditability of the journal to authenticate the research. This review also commented on the other relevant advance researches conducted in the area of AEs within clinical research as a detail comparison.

It was concluded in this review that research conducted by G. Ross Baker et.al was critical in terms of improving attention towards patient safety in clinical research and community services.
KEYWORDS

Adverse Event, ICH-GCP, Patient, Safety, Clinical Research

INTRODUCTION

This article review is based on the article, “The Canadian Adverse Events (AE) Study: the incidence of adverse events among hospital patients in Canada” published in Canadian Medical Association Journal (CMAJ) May 25, 2004 vol. 170 no. 11.

This article review begins with a literature review which briefly mentions the research topic focused in original article and other relevant aspects of the literature useful on the same research topic. Then it summarizes the article with key milestones achieved by the authors/researchers.

Further, it briefly analyses the overall structure of the article with the different key structural points talking about the flow of the research. The review also critiques the article through evaluating its authority specifying creditability of the journal in which original article was published and authors. Further it critiques on currency, accuracy, objectivity, stability and coverage of the original article.

This review article analyses the tables and figures in detail of their relevance to the actual objective of the research and relevance to the content of the original article before finally evaluating the article’s accessibility and credibility. This review article also elaborates the details of any recent advanced related topics to the original research.

The review concludes with the overall impression of the article and its usefulness in the research and any space for the improvement. Overall the article was written with clear objective and excellent interpretation of the results from performed research.

REVIEW OF LITERATURE

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH GCP Guidance E6, retrieved 2014)

Adverse events in health care are common. Most current knowledge of adverse events is based on reviews of hospital medical records, incident reports by health staff or analysis of administrative databases. These approaches each have strengths, but also inherent biases and weaknesses as many events will go unreported and unrecorded. Comparatively little is known about adverse events outside
hospitals, although some evidence suggests they may be a significant contributor to harm in health care. (Scott IA et.al, 2006)

Patient safety is receiving growing attention in community hospitals. Numerous legal cases and media stories have highlighted the consequences of unintended adverse events (AEs) recently globally. One important indicator of patient safety is the rate of AEs among hospital patients. AEs are unintended injuries or complications that are caused by health care management, rather than by the patient’s underlying disease, and that lead to death, disability at the time of discharge or prolonged hospital stays. (Brennan TA et.al, 1991) (Leape LL et.al, 1991)

Health care consumers are a relatively underused source of information about adverse events and about their views about such events. This underuse occurs despite evidence of consumers’ capability in noticing adverse events. Patient satisfaction surveys tend not to focus on adverse events so much as problems with interpersonal interactions or the delivery of care, and are most commonly conducted among inpatients. (Agoritas T et.al, 2005)

Therefore, there is a great need to increase awareness and attention towards AEs for the community health and patient safety.

**ARTICLE SUMMARY**

The purpose of the research article was to incidence of adverse events among community hospital patients in Canada. The original article clearly mentioned what were the research objectives and methodology used for the research and data analysis. The articles expressed that researchers targeted community hospitals to assess community health via wide variety of patients.

The sites selected for the research was excellent selection based on the requirements of the study design. Basic comparison and review of AE incidence with in Canadian community hospitals was done. The aim was to estimate the incidence of Adverse Events among patients in Canadian acute care hospitals. The methods used in this study are based on a protocol developed by the Harvard Medical Practice Study, which examined the incidence of AEs in New York state hospitals in 1984. (Brennan TA et.al, 1991) (Leape LL et.al, 1991)

It was specified in the article that research participants were trained; however delegation of their responsibilities within the research was really not clear. In total 20 hospitals were selected and involved for the research within 5 provinces of Canada. In total 4164 hospital admission samples (patient charts) were reviewed as a part of this research. There was no mention of consenting patient on the use of their data for the research.

This could be a potential ethical issue if not done as a part of research; although it was clear that ethical and institutional review board approval was taken for the research. The data collection was done using 2-stage review process involving patient hospital charts. The aim of the statistical analysis was very
clear to measure incidence of Adverse Events in the samples selected for the research. Kappascore
method was used for the statistical analysis

The results of the research were clearly described for patient charts reviewed in the process. Interpreta-
tion section was added in terms of traditional approach of discussion. It was readable as extension to the result section rather than actual discussion of the results. Interpretation section was clear enough to explain the results and relevance of the study results with other researchers conducted on same topic. The article concluded mentioning that additional research is needed into the incidence and types of Adverse Events beyond acute care hospital setting. The article has details of peer review and acknowledgement given to the people who participated and supported the research work.

ARTICLE STRUCTURE

The article was original based on the research conducted by the authors G. Ross Baker, Peter G. Norton, Virginia Flintoft, Régis Blais, Adalsteinn Brown, Jafna Cox, Ed Etchells, William A. Ghali, Philip Hébert, Sumit R. Majumdar, Maeve O’Beirne, Luz Palacios-Derflingher, Robert J. Reid, Sam Sheps, Robyn Tamblyn. The article was structured in following main points.

1. Abstract
2. Methods
3. Study Sample
4. Data Collection
5. Results
6. Interpretation
7. Acknowledgement
8. References

Being an original research article it had all the key and relevant sections needed to explain the research and outcomes. Detail subsections and their relativity to each other helped reader to concentrate and understand the article clearly. Article was easy to navigate. The body of article was paragraphed hence the information in each paragraph was easy to access and understand. The study design and methodology was clearly specified in the article.

The abstract was well written with subsections including background, methods, results and interpretation. Tables and figures were preciously used to describe research and outcomes. It was effective way to make readers understand research clearly.
There were sections related to the data collection and statistical analysis which elaborate how the research results were evaluated.

The article was structured through main bold points as discussed below.

- **Point 1** – What is Adverse Event (AE)?
- **Point 2** – How research in AEs is important in terms of improving patient safety?
- **Point 3** – Why patient safety needs improving attention in community?
- **Point 4** – Result outcome and relevance to other research on the same topic.

The interpretation was developed towards the end of the article. There were no separate sections for conclusion and discussion. They were combined in section for interpretation. Lack of separate conclusion section did not help readers to conclude article reading with ease.

References were cited in-text and set out clearly in the literature cited section; 18 references were given at the end which was sufficient. However, references were not listed in alphabetical order. The overall article’s structure was logically developed, with the use of detail paragraphs helping the reader access the main points more easily. The article was a PDF document.

There were links to author, journal, subjects, citations and references which allow the reader to evaluate the articles worth more effectively.

**ARTICLE CRITIQUE**

**AUTHORITY:**

The Canadian Medical Association Journal is a peer-reviewed general medical journal published by the Canadian Medical Association (CMA). It publishes original clinical research, analyses and reviews, news, practice updates, and editorials.

CMAJ platforms innovative research and ideas focused at improving health for people in Canada and globally. It publishes original clinical research, analyses and reviews, news, practice updates and thought-provoking editorials. CMAJ has had significant contribution in worldwide healthcare over the last 102 years. In Canada, the journal has played a key role in raising awareness of health and medico-social issues on topics such as the link between sun exposure and skin cancer, the dangers of smoking, contraception, abortion, euthanasia and other topics. It celebrated its 100th anniversary in 2011. (CMAJ, 2014)
The authors’ credibility was established in a number of ways. All the authors were from well-known healthcare institutes and have published number of research articles. The lead author G. Ross Bakeris a professor of Institute of Health Policy, Management and Evaluation in University of Toronto. The research was supported by Canadian Institute for Health Information and the Canadian Institutes of Health Research. (University of Toronto, 2014)

ACCURACY:

The article targeted community hospitals in the 5 different provinces of Canada covering large geographical area with 20 hospitals. The source of the information in the article was a recent research project supported by Canadian Institute for Health Information and the Canadian Institutes of Health Research. Experienced authors of the article made the article accurate and informative. The accuracy was backed up and supported by a comprehensive, recent reference list with these sources cited in-text to support both the literature review and the research itself. The strict editorial and refereeing processes of the CMAJ also contributed to the article’s accuracy.

CURRENCY:

The Canadian Medical Association Journal is a peer-reviewed general medical journal published by the Canadian Medical Association (CMA). This journal publishing research articles since last 102 years. The article was included in volume170, number 11 of 25 May 2004 while the article was accepted for publication earlier in 2004. The research review it describes was current and the article cites up-to-date references in the body of the text ranging from year 1991-2003. All the articles referenced were with latest research performed in the AE, patient safety and community health. Therefore the article is current. (CMAJ, 2014).

RELEVANCE:

This was a journal on an academic database, which has high credibility in an academic context. It was written to inform researchers, students and industrial practitioners rather than to entertain or advertise. It would be relevant to these groups but particularly any academic interested in clinical research and in community healthcare generally.

It was easy article to read and understand and therefore useful for all levels of clinical researchers and healthcare professionals. CMAJ’s articles describe innovative research and systems that help to advance medical research and to promote community health. The article was clearly a research study targeting community health and aimed to improve awareness of AEs for the patient safety. (CMAJ, 2014)

OBJECTIVITY:

The information in article was objectively developed, well supported with a current research database and with all the latest evidence acknowledged and referenced. The article objective was to study and research incidences of AEs in community hospitals and increase awareness of patient safety. There was no evidence of bias, a fact that was reinforced by the recognition that the article documents research,
which followed the rigorous research processes, and the necessary ethical considerations demanded of such intensely supported research. The supporters were clearly defined on the last page of article. The objectivity is very much clear.

STABILITY:

The article was a source of research work studying incidences of AEs within 5 provinces of Canada and increase awareness of patient safety in community hospitals. The article carefully demonstrated conducted research with the data generated during the research. The article was based on the current research in the patient safety area and backed up with practical evidences published in the recent research; therefore it's stable. The stability of the article can also be judged with the help of the authors and their creditability, expertise and work history. The Canadian Medical Association Journal and its creditability also makes article stable.

ANALYSIS OF GRAPH/IMAGE/TABLE

There were 6 (six) tables and 2 (two) figures were used to elaborate the research work in this article. All tables and figures were clearly titled and linked within the text; detail analysis of each of them is given below. Overall tables and figures were clearly defined and compliment the entire original article.

- Table 1 (page no 1679) - Table 1 shown Screening criteria applied to 3745 charts in the stage 1 review and the proportion of charts positive for each criterion. Table clearly shown numbers and percentage of charts with criterion.

- Table 2 (page no 1682) – Table 2 shown weighted and adjusted rates of adverse events (AEs), by hospital type. Point estimates and CIs were weighted to account for the total number of charts per hospital and the total number of hospitals per type per province. Whereas adjusted model was developed using backward stepwise logistic regression.

- Table 3 (page 1682) – Table 3 shown degree of physical impairment or disability at discharge resulting from AEs, as determined by physician reviewers, by hospital type.

- Table 4 (page 1683) – Table 4 shown association of AEs with length of stay (LOS), by hospital type. Physician reviewers were asked to estimate, on the basis of their professional judgment, the number of additional days in hospital directly related to AEs.

- Table 5 (page 1683) - Table 5 shown procedures or events to which AEs were related, by service most responsible services such as medicine and surgery for delivery of care at time of AE.

- Table 6 (page 1684) - Table 6 shown studies of AEs in hospital patients. Table was very comprehensive providing data on the studies in hospitals and associated AEs.
Figure 1 (page1681) – Figure 1 was flowchart of review process for the Canadian Adverse Events (AEs) Study. It was very clear figure to explain 2 stage approach used for this research.

Figure 2 (page 1682) – Figure 2 was of timing and occurrence of AEs relative to index hospital admission. It has clearly shown AEs occurrences related to the time.

RECENT ADVANCES RELATED TO THE TOPIC

There were few recent researches conducted on AEs incidences and patient safety in healthcare and community hospitals. Few recent topics are discussed below.

A study conducted by Aranaz-Andrés JM et.al on “Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events” concluded that the incidence of patients with AE related to medical assistance in Spanish hospitals was relevant and similar to those found in the studies from Canada and New Zealand that had been conducted with comparable methodology. Patient vulnerability has been identified therein as playing a major role in generating healthcare-related AEs. These and other recent results indicate the need for AEs to be considered a public health priority in Europe. (Aranaz-Andrés JM et.al, 2008)

Another study conducted by Masotti P et.al on “Adverse events in community care: developing a research agenda”. The study describes the results of a consensus workshop in which 31 healthcare professionals were asked to identify and rank common adverse events and important research questions relating to community care. Workshop participants were decision-makers and healthcare providers with areas of expertise that included community and home care; acute and primary care; patient safety; medical errors; and health services policy, administration and research. Results include prioritized lists of adverse events, research questions and contributing factors associated with adverse events. (Masotti P et.al, 2007)

A study was conducted by Robert JA et.al in 2009 on “Self-reported adverse events in health care that cause harm: a population-based survey” concluded that an incidence of self-reported harmful adverse events that was significantly lower than that found by a 2002 Australian survey. Better communication to help patients acquire more realistic risk perception may help reduce harm. Better communication could also increase public advocacy for systems improvement in safety to counter persisting community beliefs that individual action alone can redress the situation.
CONCLUSION

The research discussed in the original article “The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada” was with clear objective and a true research. The content, structure, strengths and limitations of the article were analyzed and critiqued. The article has contributed to the literature in terms of its valuable research of AE incidences in 5 different provinces across 20 hospitals and challenges in awareness of patient safety. The article was very good reference information based on the practical and current research. It had all the details revolving around increasing attention of patient safety, their challenges and usefulness along with certain limitations.

The article expressed detail picture and true data on AE incidences and its effective use which is critical for improving attention to patient safety in community health and healthcare research in current era. The article was very well written and had all the necessary sections to discuss the detail research conducted and outcome obtained. Tables and figures included in the article were accurate, and clear for understanding. It was very useful and informative article for the academic and healthcare researchers. It is suggested to add some more definitive details on the future policies and research directions for the readers and researchers. A conclusion section highlighting key conclusions would be useful in the article.

REFERENCE


DISCREPANCIES AND INADEQUATE REPORTING IN RANDOMIZED CLINICAL TRIALS OF TRADITIONAL CHINESE MEDICINE (TCM)

A Case Study By Ahmed Mohamed Ali Yousif, Sudan
(M.Sc CR, PhD in Clinical Research Student of Texila American University)
Email: ayousif@phcc.gov.qa

SOURCES

ABSTRACT
Background: Bias might occur due to the clinical research study structures, endogenous bias, and to the investigators’ intention, external bias, on selecting only the positive outcomes and published them. So the publication bias still widespread in TCM clinical, but TCM are not unique cases, therefore study conclusions ought to be interpreted with caution.

Objective: to review the article “Prospective registration, bias risk and outcome-reporting bias in randomized clinical trials of traditional Chinese medicine: an empirical methodological” regarding the contents, strengths, structures and limitations of Traditional Chinese Medicine (TCM) Clinical trials. In addition to outcome-reporting bias in randomized clinical trials.

Results: The number of Chinese randomized trials registration increases from 1999 to 2012, as well as the countries where these Chinese trials registered. As well as the frequency of the type of TCM intervention included in each registry. Classification of disease based on the International Classification of Diseases (ICD-10) has been used to classify medical conditions. Only (46.1%)= 505 out of 1096 registered randomized trials were completed studies. Only has found 29% of registered TCM trials presented selective outcome-reporting bias in between the outcomes registered and the outcomes published.
Conclusions: The quality of TCM clinical trials have developed through prospective international trial registration compared with previous methodological studies. Although there are some inconsistencies between the registered trial protocols and subsequent publications and inadequate reporting. Nevertheless it is indistinct how the study designs have got better-quality.

KEYWORDS
Chinese Medicine, Clinical Trials, Acupuncture, Conventional Medicine, Medical Journals, Herbal Medicine

INTRODUCTION
This review critically reviews the article ‘Prospective registration, bias risk and outcome-reporting bias in randomized clinical trials of Traditional Chinese Medicine (TCM): an empirical methodological study ‘published in 16 July 2013 in The British Medical Journal (BJM open).

Publication bias as a consequence of selective outcome reporting is still widespread and similar to conventional medicine. In herbal medicine trials, it would be inappropriate if a trial design does not utilize syndrome differentiation, and participants may not be properly treated.

“Syndrome differentiation (Bian Zheng) in traditional Chinese medicine (TCM) is the comprehensive analysis of clinical information gained by the four main diagnostic TCM procedures: observation, listening, questioning, and pulse analysis, and it is used to guide the choice of treatment either by acupuncture and/or TCM herbal formulae”. 1

The review will first include a literature review. Secondly, will summarize the article. Thirdly, it will briefly analyze the article in order to see if the information in the article is quite enough to disclose how the TCM empirical studies methodological quality of randomized clinical trials carried out , avoiding the risk of external and external biases. Fourthly, the review will critique the article through evaluating its authority, currency, accuracy, objectivity, stability and coverage. The review will also analyze the tables before finally evaluating the article’s accessibility and credibility.

REVIEW OF LITERATURE
TCM has long been herbal medicine used to treat diabetes2, diabetic peripheral neuropathy, gastrointestinal disorders including irritable bowel syndrome3, non-operative therapy to treat small-bowel obstruction (SBO) 4, HIV infection and AIDS5, viral myocarditis6 and etc. Also, some conventional non-pharmacological and pharmacological treatments for insomnia used as an alternative therapy such as acupuncture7. There are others traditional Chinese non-pharmacological treatments
like; moxibustion, cupping, tuina, qigong, tiaichi, guasha, etc8, have been used to treat diseases and medical condition.

There is increased numbers of clinical trials investigating a variety of TCM interventions have been registered in international trial registries. Publications on TCM trials are uniformly positive a matter that raised the concerns to investigate the TCM which published if they have positive results. One of the ways to improve trial quality is to prospectively register clinical trial protocol in international trial registers such as clinical trials.gov, international clinical trial registry platform, established by World Health Organization (WHO) in 2005. In addition to that there are several peer –reviewed journals such as Lancet and Trials.

The object of the study in this article stated strengths and limitations ;1- systemic searches of all available international trial registries for any clinical trials of TCM .2- all interventions involving any TCM were included as was the diagnosis,3- the registered information for clinical trials not uniform across the registries and important methodological information may be missing, 4- subsequent publications were obtained for those studies recorded as ‘ completed ‘ in the registry. This may not represent the true situation for trials if the registry data not updated by the researchers. The study design of registered TCM trials has improved in estimating sample size, use of blinding and placebos. However, selective outcome reporting is widespread and similar to conventional medicine and therefore study conclusions should be interpreted with caution.

ARTICLE SUMMARY

TCM has long been used to treat a number of diseases and medical conditions with pharmacological and non–pharmacological treatments. The clinical data of TCM specialty and treated disease/conditions extracted from the registries and searched for subsequent publications in PubMed and Chinese databases. Then, TCM clinical trials in registries were systematically assessed and evaluated, and also their subsequent publications. Also, the characteristics of TCM trials were estimated for bias risk and outcome-reporting bias.

Fifteen trial registries were searched from their inauguration to July 2012 to identify randomized trials on TCM which included treatments with herbs, acupuncture and/or moxibustion, cupping, tuina, qigong, etc.

The information in the registries of completed trials compared with their publications focusing on study design, sample size, randomization, and bias risk including reporting bias from the register protocol.

Publication bias as a consequence of selective outcome reporting is still widespread and similar to conventional medicine, therefore study conclusions should be interpreted with caution. In herbal medicine trials, it would be inappropriate if a trial design does not utilize syndrome differentiation, and participants may not be properly treated.
The article finalized that the study design and the quality of reporting of TCM trials have improved through prospective international trial registration compared with previous methodological studies, although there are some inconsistencies between the registered trial protocols and subsequent publications and insufficient reporting on syndrome differentiation.

**ARTICLE STRUCTURE**

The article was introduced with an abstract providing a brief overview of main points in the original study as well as an article summary emphasizing article focus, key message of article and strengths and limitations of this study. The paragraphs were of suitable lengths and the idea in each one was well developed and the information was easy to access. The background or the introduction to the article came immediately without special heading after the conclusion of the abstract.

Then and there were six headings, which meant that there was a lot of quite detailed information contained under each heading. The six sections include; methods, inclusion and exclusion criteria. Any TCM clinical trials with singly or combined intervention were included. Non-randomized such as quasi randomized studies, cohort, phase trial, retrospective studies were excluded. The method explained that there were no limitations on study type.

Data source; any TCM trial listed as ‘completed’ in the registered records of a 15 major international trial registries (14 linked to WHO –International clinical trial registry platform from their inception to July 2012. Other sources; articles published in PubMed, three Chinese Electronic Bibliographic Database, China National Knowledge Infrastructure and Chinese VIP Information.

The data extracted from each trial registry by two researchers using a standard, piloted data extraction form which was based on general characteristics of clinical trials, methodology and the 20minimum items required for WHO trial registration. The main information collected included all the information that have to be in research protocol and ethics required to carry out the researches. Results of the study summarized in flow diagram and figure and four tables. The article was well developed and it was HMLT rather than scanned PDF document and include many links that help to make the information accessible. Authors, citation, references journals and subjects links were provided to the readers.

**ARTICLE CRITIQUE**

**AUTHORITY**

BMJ is a weekly open-access 9 peer-reviewed medical journal. Open access (OA) is the practice of providing unrestricted access via the Internet to peer-reviewed scholarly research. BJM is one of the world's oldest general medical journals and has been described as among the most prestigious10. Originally called the British Medical Journal, the title was officially shortened to BMJ in 1988.
The journal is published by the BMJ Group, a wholly owned subsidiary of the British Medical Association. It has publication history from 1840 to present. The author’s credibility established in; they have affiliations of some of the universities, institution, centers and hospital in China, UK, Germany, USA and Denmark. The article was published in peer-reviewed journals and data of the study extracted from major international trial registries.

**ACCURACY**

The final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 3.0 License. So the research was current project. It was backed up and supported by comprehensive and recent 16 references. All authors have read and approved the final manuscript. Authors; J.PL, MH, X-XK, Y-JM, Y-YW and G-YY were supported by the grant number 2011-CXTD-09 from Beijing University of Chinese Medicine. BB, J-PL and EM were partially funded by the grant number R24 AT001293 from the National Institutions of Health. J-PL and MH were partially funded by the grant number 2011ZX09302-006-01-03(5) by the Ministry of Science and Technology of China.

Author affiliations and refereeing processes also contributed to the article’s accuracy as did the links to other expert sources; http://bmjopen.bmj.com.http://dx.doc.org/10.1136/bmjopen-2013-002968).

**CURRENCY**

The prepublication history and additional material for this article is available online. The article received in 1 April 2013, revised 31 May 2013 and accepted 17 June 2013. Therefore the research was current and the article cited up–to-date references in the body of the text ranging from 1998-2011. The journal has publication history from 1840 to present, and the article was accepted for publication in 17 June 2013.

The study’ Prospective registration, bias risk and outcome-reporting bias in randomized clinical trials of Traditional Chinese Medicine (TCM): an empirical methodological study. These trial assessed with current measures to evaluate their ability to answer the contemporary concerns of clinicians and care provider.

**RELEVANCE**

The article concluded that the study design and the quality of reporting of TCM trials have improved through prospective international trial registration compared with previous methodological studies. The article stated that: there are some inconsistencies between the registered trial protocols and subsequent publications and insufficient reporting on syndrome differentiation. Selective outcome reporting in TCM in publications is still widespread, careful interpretation for a study’s conclusion is necessary.

In TCM herbal medicine trials, it would be inappropriate if the trial design does not utilise syndrome differentiation, and participants may not be properly treated. The article
Did not explain the meaning of the terminology of syndrome differentiation, a matter that might little bit difficulty to some readers to understand one the most important entity the TCM based to treat different diseases with same medicine and same disease with different treatments.

**OBJECTIVITY**

The information regarding the TCM was objectively developed; there are increasing numbers of clinical trials investigating a variety of TCM interventions have been registered in international trial registries and this supported with a current base with all evidence acknowledged and referenced.

The article disclosed that the study has some limitations; A- lack of standardized of the items required for registration in different registry: B- research only carried for ‘completed ‘and published trial of TCM, C-research undertook in PubMed and three Chinese databases only, there is lag time between completing a study and writing for publication, D- very large number of TCM trials were conducted without being registered, nothing could be said about their risks of random errors. Finally, it could be concluded that TCM trial have improved through prospective international trial registration compared with previous method logical studies.

**STABILITY**

Stability is supported by criteria of inclusion, exclusion, data sources, data extraction of the article, and being published in 16 July 2013 in BJM open. With its sources of 15 major international trial registries, 14 of them linked to WHO ICTRP from their inception to July 2012 and three Chinese electronic bibliographic databases.

**ANALYSIS**

The article contained a flow diagram, figure 1, consisted of boxes that connected to one another, the boxes summarized the procedure used, from the sources of the data through the criteria of inclusion and exclusion to analysis. The Diagram supported with a key explained the abbreviation used. Figure 2 in the article showed the number of registered trials from the year 1999 to 2012, as well as the countries where these Chinese trials registered. Table 1 summarized the registered and randomized trials on TCM by registry and countries. It contained all the types of the randomized trials in TCM that valid for the purpose of the study "Table 1 shows the frequency of the type of TCM intervention included in each registry" Each registry is not shown in table 1, only the country of TCM intervention.

Table 2 illustrates all the disease and medical conditions studied in the completed registered TCM. Classification of disease based on the International Classification of Diseases(ICD-10). Table 3 gave information of the methodological of only1096/1640 registered randomized trials were identified evaluating TCM, of which 505 were completed studies (46.1%). Table 3 does not show the variation across registries, only the methodological variation across TCM interventions.
International Trial Registries. Table 4 constructed to illustrate if there is any reporting – bias in the methodological components between registered records and subsequent publications of RCTs.

CONCLUSION

The aim of this review is to review the article of ‘Prospective registration, bias risk and outcome-reporting bias in randomized clinical trials of traditional Chinese medicine: an empirical methodological study’. The contents, strengths, structures and limitations were analyzed and critiqued. The article has contributed to the literature in terms of its valuable critique of current research measures that govern study on clinical trials and to investigate a variety of TCM interventions which have been registered in international trial registries

The study design of registered TCM trials has improved in estimating sample size, use of blinding and placebos. There are increasing number of clinical trial investigated TCV registered in international registries Bias might occur due to the clinical research study structures, endogenous bias, and to the investigators’ intention, external bias, on selecting only the positive outcomes and published them.

So the publication bias still widespread in TCM clinical, but TCM are not unique cases, therefore study conclusions ought to be interpreted with caution. In herbal medicine trials, it would be inappropriate if a trial design does not utilize syndrome differentiation, and participants may not be properly treated. The article concluded that the quality of TCM trials have improved through prospective international trial registration compared with previous methodological studies. Although there are some discrepancies between the registered trial protocols and subsequent publications and insufficient reporting on syndrome differentiation. But it is unclear how the study design has improved.

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INTEGRATED APPROACH TO HEALTH CARE MANAGEMENT BY STAKEHOLDERS

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INTRODUCTION

The term ‘Stakeholder’ is a broad term that applies to:

People inside the organization, but usually outside of the project team, who are in some way affected by the project. Typically Stakeholders will be users of the output from a project or benefit from its introduction. They may also have to change their role, function or method of working as users of new systems, processes or products.

Stakeholders might also be external customers and suppliers, as they might be directly affected by the changes resulting from a project. Stakeholders could include those who identified the need for project activity.

KEYWORDS

Stakeholder, Project Development, Healthcare, Researchers, Population, Customers

ARTICLE SUMMARY

A “stakeholder” in a worker health study is an individual or a group with an interest, or “stake” in the conduct or outcome of the study. When workers participate in research studies, the list of stakeholders is long and includes, at a minimum, workers, the employer, insurers, researchers and their institutions, multiple levels of government, funding agencies, the public/community, unions, Institutional Review Boards (IRBs), and occupational medical professionals.
The concerns and issues important to each stakeholder are listed in this section. These should be noted and addressed early in the research planning to ensure their inclusion in the overall design, conduct, and publication of the study.

**REVIEW OF LITERATURE**

**STAKEHOLDER'S RESPONSIBILITIES**

These depend on the position of the Stakeholder in the context of the project development and implementation but typically could include the following responsibilities:

- understanding the business rationale and ensuring that the project fits with the strategy for their area of business
- making their detailed requirements known
- committing the necessary resources to ensure the project is successful
- taking ownership of appropriate deliverables
- keeping informed of project progress and cascading information to others who need to know
- proactively establishing training and development requirements
- approving key project deliverables
- Identifying and resolving any project issues and risks, especially those associated with managing change during the transition phase.

The preeminent concern for all stakeholders is the protection of the rights and Welfare of worker-subjects in research studies. Stakeholder concerns may include access to workers (the researchers), maintaining productivity in the workplace (the employer), and assuring compliance with federal regulations (federal authorities).

Thus, there is the potential for conflict among groups of stakeholders, and such conflict may not always be in the best interests of the worker. There is a need to balance the proposed research with each stakeholder’s interests. Several considerations are important in protecting the rights and well-being of study subjects and assuring that stakeholders in the studies are able to protect valid interests.

These include:
• Recognizing the diverse interests and concerns of other stakeholders.

• Clarifying responsibilities of all participants.

• Agreeing to work cooperatively with one another to achieve the best possible results for the study and all participants.

INTERESTS, CONCERNS, AND RESPONSIBILITIES

There are interests, concerns, and responsibilities shared by all stakeholders that should be acknowledged, accepted, and/or agreed upon during the initial planning stages of the worker health study and re-examined throughout the study process.

SHARED INTERESTS AND CONCERNS APPLICABLE TO ALL STAKEHOLDERS ARE TO ENSURE:

• The protection of the rights and welfare of worker-subjects.

• Early notification all stakeholders particularly the worker population of studies.

• Early involvement of all stakeholders, including the worker population, in the design and development of the study.

• All stakeholders understanding the objectives and proposed methods of the study.

• All stakeholders understand and comply with human-subject study ethics and Regulations.

Shared responsibilities applicable to all stakeholders are:

• To ensure that the study has scientific merit and/or is subject to rigorous peer review.

• To be informed about the research topic and procedures.

• Work to achieve consensus with other stakeholders when conflicts are apparent.

• To provide notification and project information to other stakeholders.

• To participate actively in the development, design, and conduct of the study.

• To fulfill these responsibilities throughout the life of the study.
Stakeholders in worker studies share responsibilities to recognize one another’s interests and concerns, to clarify their own individual responsibilities, and to agree to work cooperatively with one another to achieve the best possible results for all parties.

Each stakeholder involved in worker studies is ultimately responsible for fully understanding his or her role in protecting workers who are subjects of research.

The issues, concerns, and responsibilities specific to individual stakeholders are described below.

Workers have the most to gain and lose from worker studies. Their interests and concerns should take precedence over the interests and concerns of other stakeholders.

Interests and concerns applicable to workers and worker-subjects include:

• The freedom from coercion/pressure to participate, decline or withdraw—whether real or perceived.
• Perceived or actual threats to job security, future employability, Pension or medical benefits.
• Early and complete notification of studies planned or conducted.
• A full understanding of the research protocol and purpose.
• Privacy and confidentiality of personal records, data, or tissues.
• The possible perception of being exploited when they are the subject of an excessive number of research studies (considered as guinea pigs).
• Job security and potential impact on job advancement.
• The extent of involvement in the program.
• The impact of time away from job or lost time.
• Possibility of injury or pain.
• Possibility of psychological impact.
• Continued or future insurability.
• Potential impact on family.
• Potential social stigma (personal or family).
• The availability of counseling.
• An awareness of available methods to resolve concerns.

• Read pertinent study information.

• Read and understand the informed consent documents and study materials.

• Know and understand one’s rights as a research subject.

• Abide by protocol (if the individual agrees to participate in the study).

• Confirm that they understand the subject matter with study experts.

THE ABILITY AND RESOURCES TO EDUCATE STAKEHOLDERS IN THE REQUIREMENTS

• The ability to adequately protect workers involved in projects conducted by other agencies.

• The ability to fully assess similar studies being done by other agencies on the site.

• The ability to enforce regulatory expectations.

• Mechanisms for being notified of human subjects studies that have been proposed to be conducted at the site.

• That it gives the same attention to non-physical (social) risks to workers as it does to physical risks.

• Mechanisms to ensure that the researchers adhere to the approved protocol, and notify the institution of changes or adverse events.

• The authority to terminate research that does not adhere to the approved protocol.

• The assurance that the membership of the local IRB reflects all stakeholders’ Interests.

• An assessment and assurance of the scientific merit of the research.

Many different groups have an interest or involvement in digital information. Any strategy for digital preservation will naturally have to take into account the various needs and perspectives of these groups.

The stakeholders include:

• Authors
• Publishers
• Libraries
• Archive centres
• Distributors
• Networked information service providers
• IT suppliers
• Legal depositaries
• Consortia
• Universities
• Research funders

Stakeholder Interest and impact on the long term preservation of digital material Initiators Collection development. Research libraries collect material that is current, published on current technology. Establish the nature and scale of the threat of irretrievable loss for digital material items.

Regulators Legal deposit; Public Record Office; Copyright. Legislation to preserve ownership for a limited period of time, to ensure a national collection of material is established and to preserve items that are in the public interest.

Creators Creation of digital records. Lack of control over format of deposited items leads to unmanageable diversity. Rights owners maintain copyright. Preservation of material may lead owners to demand copyright in perpetuity.

Fund-holders manage the funds available for preservation activity according to agreed priorities and service levels. Providers Initial diversity of formats at publication complicated by new editions in new formats and on new media.

Readers Access to material. Readers will demand material in current acceptable format for display and inclusion in new digital material. Archivists Conserve the archive, whilst preserving the items, and maintain the integrity of the deposited items.

Providers Provide new editions, which link into the new intellectual context through re-indexing and re-packaging. Interferers Make material inaccessible through technological turbulence or blocking publication.
A relative newcomer to the scene are the interferers. They may be seen as the antithesis of the regulators — although new regulations may be brought in to counter their activities. Sometimes they may simply be a nuisance, obstructing the course of good preservation practice, taking a narrow perspective on minor issues, or delaying the introduction of new measures. At other levels their effects may be far-reaching.

Budget cuts, for example, can seriously damage the value of a collection, by restricting intake and causing holdings to be disposed of. Political instability can destroy centuries of preservation — the intellectual heritage of a culture.

Attitudes of the stakeholders to the preservation of digital data, in terms of both their needs and their responsibilities. They need to be identified prior to the project proposal being discussed, and be the driving force and sponsor for the project through all stages from development to training, implementation and support.

The key stakeholder is a pivotal role in the success of any project and they have a number of core responsibilities that they must adhere to.

**UNDERSTANDING THE BUSINESS DRIVERS AND ENSURING THAT THE PROJECT FITS WITH THE STRATEGY FOR THEIR AREA OF THE BUSINESS:**

A fundamental responsibility – the stakeholder must be able to clearly explain the necessity for their project to be taken on before others and prove its strategic merit.

**PROVIDING DETAILED REQUIREMENTS AND A FINANCIAL PLAN:**

Every project must have these and is doomed to fail if they’re not completed up front.

**COMMITTING THE NECESSARY RESOURCES:**

It’s key to have individuals from the affected areas involved on any project. They can provide you with instant answers and feedback as to how things do or should work. They are the daily operational link to the eventual user base of the project deliverables and I cannot stress enough the importance and usefulness of having them involved. Agile PM methodologies allow you to have quicker bursts of development and a higher pace of deliverable but if you are using traditional project management
techniques and don’t have target resources available, you could be wasting a whole heap of time and reputation if your deliverables don’t match what the client wants.

**TAKING OWNERSHIP OF APPROPRIATE DELIVERABLES:**

The stakeholder needs to take ownership of the appropriate deliverables and make sure that they work against a number of key elements such as mirroring the requirements, process compatibility, usability and performance. They must sign off and take ownership of each deliverable, thus allowing the project to proceed on the right track.

**KEEPING ABR EAST OF PROJECT PROGRESS AND CASCADING INFORMATION TO OTHERS WHO NEED TO KNOW:**

The stakeholder must not skip project meetings and rely upon others to keep them up to speed. Similarly, they must also keep affected others or teams up to date with frequent progress reports. This is probably the most oft-reported symptom of failed projects where key stakeholders become disassociated with a project and it starts to drift, stray from the requirements and fall apart. Stakeholders must stay focused and attend all key project meetings.

**ESTABLISH THE TRAINING AND SUPPORT REQUIREMENTS:**

The stakeholder must identify any affected individuals of their projects and establish the necessary training and support requirements. This will be done in harness with the relevant departments but the stakeholder is responsible for it. A project should not end when the development is finished but when it is fully implemented with full training and relevant support models.

**IDENTIFYING AND RESOLVING ANY PROJECT ISSUES AND RISKS, ESPECIALLY THOSE ASSOCIATED WITH MANAGING CHANGE DURING THE TRANSITION PHASE:**

It’s up to the stakeholder to identify and acknowledge any potential risk and change associated with their project during the proposal stages. This will obviously be discussed with the project team, PMO or legal representatives prior to the project getting a green light.
COMMUNICATING THROUGHOUT THE LIFE OF THE PROJECT:

I cannot stress enough the need for strong communication. The least successful projects are the ones that are done in isolation that people forget about until an email gets sent around heralding its imminent implementation. Requirements or processes sometimes change during project development and without having relevant resource or communication with the targeted business areas; a project will quickly lose resonance and relevance. Managing associated change during the transition phase must be done up front or during the life of the project and not when it is ready to be implemented as those reticent to change can quickly sour any implementation.

Project closure:

In accordance with good project governance, the stakeholder must perform an analysis of the projects delivery against plan, budget and strategic objectives and sign off and accept the project.

Article Structure

This article structured in such a way it reveals what all roles and responsibilities do stakeholders carry out.

Article Critique

Accuracy

This article is accurate in its data base. It is being followed and practiced presently.

Relevance

This article is relevant and can be followed during any drug is about to be introduced.

Stability

The article, with its source an academic journal on an academic data base is stable as a resource.

CONCLUSIONS

There is always a danger that surveys will over-represent those with an interest in the topic and that conclusions will be based on a self-selecting, unrepresentative minority, despite strenuous efforts to avoid this outcome. The views of non-respondents are likely to be just as interesting as the contributions of those who did participate — if only we could get at them.
Nevertheless, it is possible to draw some broad conclusions about the perspectives on digital preservation of both communities.

1. There is concern across all sectors that resources are being lost and agreement on the need for a campaign to promote awareness of data preservation.

2. There is an acknowledgement of the role of the creators of digital information and their responsibility for its long-term preservation. This is linked to concerns about the ownership of digital material and the protection of intellectual property rights.

3. There is common concern about the costs of preservation, especially since the scale of costs involved is an unknown factor.

4. There is no consensus, however, on how digital preservation might be financed, although many indicate that some form of national funding is necessary.

5. There is also agreement on the need for collaborative developments, and for shared and agreed policies.

6. All express the need for guidance — a national policy and guidelines covering preservation of electronic materials. Many feel that a central national body should lead on preservation policy and monitor all relevant developments in standards and best practice.

7. Overall there is a lack of established policies and guidelines and evidence to suggest that the majority of organizations have not thought through the implications of digital preservation. Clearly, there are exceptions to this, and it is to those organizations which have taken a lead that we must look for examples of best practice.

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SYSTEMATIC REVIEW: AN APPROACH FOR TRANSPARENT RESEARCH SYNTHESIS

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ABSTRACT

A systematic review is a literature review focused on a research question that tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question. Systematic reviews of high-quality randomized controlled trials are crucial to evidence-based medicine. An understanding of systematic reviews and how to implement them in practice is becoming mandatory for all professionals involved in the delivery of health care. Besides health interventions, systematic reviews may concern clinical tests, public health interventions, social interventions, adverse effects, and economic evaluations. Systematic reviews are not limited to medicine and are quite common in other sciences where data are collected, published in the literature, and an assessment of methodological quality for a precisely defined subject would be helpful.

With an ever-increasing plethora of studies being published in the health sciences, it is challenging if not impossible for busy clinicians and researchers alike to keep up with the literature. Reviews summarizing the outcomes of various intervention trials are therefore an extremely efficient method for obtaining the “bottom line” about what works and what doesn’t.
In his review we cover the basic principles of Systemic review and meta-analysis. The important issues that needs to consider while doing systematic reviews and meta-analysis are outlined and some of the terms used in the reporting of systematic reviews and meta-analysis such as odds ratio, relative risk, confidence interval and forest plot

KEYWORDS

Systemic review, Randomized trial, meta-analysis, clinical research
INTRODUCTION

A systematic review aims to provide an exhaustive summary of current literature relevant to a research question. The first step of a systematic review is a thorough search of the literature for relevant papers. The Methodology section of the review will list the databases and citation indexes searched, such as Web of Science, Embase, and PubMed, as well as any hand searched individual journals. Next, the titles and the abstracts of the identified articles are checked against pre-determined criteria for eligibility and relevance. This list will always depend on the research problem. Each included study may be assigned an objective assessment of methodological quality preferably using a method conforming to PRISMA (the current guideline) or the high quality standards of Cochrane collaboration.

Systematic reviews often, but not always, use statistical techniques (meta-analysis) to combine results of the eligible studies, or at least use scoring of the levels of evidence depending on the methodology used. An additional rater may be consulted to resolve any scoring differences between raters. Systematic review is often applied in the biomedical or healthcare context, but it can be applied in any field of research. Groups like the Campbell Collaboration are promoting the use of systematic reviews in policy-making beyond just healthcare.

A systematic review uses an objective and transparent approach for research synthesis, with the aim of minimizing bias. While many systematic reviews are based on an explicit quantitative meta-analysis of available data, there are also qualitative reviews which adhere to the standards for gathering, analyzing and reporting evidence. The EPPI-Centre has been influential in developing methods for combining both qualitative and quantitative research in systematic reviews.

Recent developments in systematic reviews include realist reviews and the meta-narrative approach. These approaches try to overcome the problems of methodological and epistemological heterogeneity in the diverse literatures existing on some subjects. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement suggests a standardized way to ensure a transparent and complete reporting of systematic reviews, and is now required for this kind of research by more than 170 medical journals worldwide.

Health care professionals are increasingly required to base their practice on the best available evidence. In the first article of the series, I described basic strategies that could be used to search the medical literature. After a literature search on a specific clinical question, many articles may be retrieved. The quality of the studies may be variable, and the individual studies might have produced conflicting results. It is therefore important that health care decisions are not based solely on one or two studies without account being taken of the whole range of research information available on that topic.

Health care professionals have always used review articles as a source of summarized evidence on a particular topic. Review articles in the medical literature have traditionally been in the form of “narrative reviews” where experts in a particular field provide what is supposed to be a
“summary of evidence” in that field. Narrative reviews, although still very common in the medical field, have been criticized because of the high risk of bias, and “systematic reviews” are preferred. Systematic reviews apply scientific strategies in ways that limit bias to the assembly, a critical appraisal, and synthesis of relevant studies that address a specific clinical quest.

THE PROBLEM WITH TRADITIONAL REVIEWS

The validity of a review article depends on its methodological quality. While traditional review articles or narrative reviews can be useful when conducted properly, there is evidence that they are usually of poor quality. Authors of narrative reviews often use informal, subjective methods to collect and interpret studies and tend to be selective in citing reports that reinforce their preconceived ideas or promote their own views on a topic. They are also rarely explicit about how they selected, assessed, and analyzed the primary studies, thereby not allowing readers to assess potential bias in the review process. Narrative reviews are therefore often biased, and the recommendations made may be inappropriate.

WHAT IS A SYSTEMATIC REVIEW?

In contrast to a narrative review, a systematic review is a form of research that provides a summary of medical reports on a specific clinical question, using explicit methods to search, critically appraise, and synthesize the world literature systematically. It is particularly useful in bringing together a number of separately conducted studies, sometimes with conflicting findings, and synthesizing their results.

By providing in a clear explicit fashion a summary of all the studies addressing a specific clinical question,4 systematic reviews allow us to take account of the whole range of relevant findings from research on a particular topic, and not just the results of one or two studies. Other advantages of systematic reviews have been discussed by Mulrow. They can be used to establish whether scientific findings are consistent and generalisable across populations, settings, and treatment variations, or whether findings vary significantly by particular subgroups. Moreover, the explicit methods used in systematic reviews limit bias and, hopefully, will improve reliability and accuracy of conclusions. For these reasons, systematic reviews of randomised controlled trials (RCTs) are considered to be evidence of the highest level in the hierarchy of research designs evaluating effectiveness of interventions.
METHODOLOGY OF A SYSTEMATIC REVIEW

The need for rigour in the preparation of a systematic review means that there should be a formal process for its conduct. Below figure 1 summarizes the process for conducting a systematic review of RCTs. This includes a comprehensive, exhaustive search for primary studies on a focused clinical question, selection of studies using clear and reproducible eligibility criteria, critical appraisal of primary studies for quality, and synthesis of results according to a predetermined and explicit method.

**Figure 1:** Methodology for a systematic review of randomised controlled trials.
WHAT IS A META-ANALYSIS?

Following a systematic review, data from individual studies may be pooled quantitatively and reanalysed using established statistical methods. This technique is called meta-analysis. The rationale for a meta-analysis is that, by combining the samples of the individual studies, the overall sample size is increased, thereby improving the statistical power of the analysis as well as the precision of the estimates of treatment effects.

Meta-analysis is a two stage process. The first stage involves the calculation of a measure of treatment effect with its 95% confidence intervals (CI) for each individual study. The summary statistics that are usually used to measure treatment effect include odds ratios (OR), relative risks (RR), and risk differences.

In the second stage of meta-analysis, an overall treatment effect is calculated as a weighted average of the individual summary statistics. Readers should note that, in meta-analysis, data from the individual studies are not simply combined as if they were from a single study. Greater weights are given to the results from studies that provide more information, because they are likely to be closer to the “true effect” we are trying to estimate. The weights are often the inverse of the variance (the square of the standard error) of the treatment effect, which relates closely to sample size.12 The typical graph for displaying the results of a meta-analysis is called a “forest plot”.

THE FOREST PLOT

The plot shows, at a glance, information from the individual studies that went into the meta-analysis, and an estimate of the overall results. It also allows a visual assessment of the amount of variation between the results of the studies (heterogeneity). Figure 2 shows a typical forest plot. This figure is adapted from a recent systematic review and meta-analysis which examined the efficacy of probiotics compared with placebo in the prevention and treatment of diarrhoea associated with the use of antibiotics.
**Figure 2:** Effect of probiotics on the risk of antibiotic associated diarrhoea

**DESCRIPTION OF THE FOREST PLOT**

In the forest plot shown in fig 2, the results of nine studies have been pooled. The names on the left of the plot are the first authors of the primary studies included. The black squares represent the odds ratios of the individual studies, and the horizontal lines their 95% confidence intervals. The area of the black squares reflects the weight each trial contributes in the meta-analysis. The 95% confidence intervals would contain the true underlying effect in 95% of the occasions if the study was repeated again and again. The solid vertical line corresponds to no effect of treatment (OR=1.0).

If the CI includes 1, then the difference in the effect of experimental and control treatment is not significant at conventional levels (p>0.05). The overall treatment effect (calculated as a weighted average of the individual ORs) from the meta-analysis and its CI is at the bottom and represented as a diamond. The centre of the diamond represents the combined treatment effect (0.37), and the horizontal tips represent the 95% CI (0.26 to 0.52). If the diamond shape is on the Left of the line of no effect, then Less (fewer episodes) of the outcome of interest is seen in the treatment group. If the diamond shape is on the Right of the line, then moRe episodes of the outcome of interest are seen in the treatment group. In fig 2, the diamond shape is found on the left of the line of no effect, meaning that less diarrhoea (fewer episodes) was seen in the probiotic group than in the placebo group. If the diamond touches the line of no effect (where the OR is 1) then there is no statistically significant difference between the groups being compared. In fig 2, the diamond shape does not touch the line of no effect (that is, the confidence interval for the odds ratio does not
include 1) and this means that the difference found between the two groups was statistically significant.

APPRAISING A SYSTEMATIC REVIEW WITH OR WITHOUT META-ANALYSIS

Although systematic reviews occupy the highest position in the hierarchy of evidence for articles on effectiveness of interventions, it should not be assumed that a study is valid merely because it is stated to be an systematic review. Just as in RCTs, the main issues to consider when appraising a systematic review can be condensed into three important areas.

- The validity of the trial methodology.
- The magnitude and precision of the treatment effect.
- The applicability of the results to your patient or population.

Box 1 shows a list of 10 questions that may be used to appraise a systematic review in all three areas.16

- Did the review address a clearly focused question?
- Did the review include the right type of study?
- Did the reviewers try to identify all relevant studies?
- Did the reviewers assess the quality of all the studies included?
- If the results of the study have been combined, was it reasonable to do so?
- How are the results presented and
- What are the main results?
- How precise are the results?
- Can the results be applied to your local population?
- Were all important outcomes considered?
- Should practice or policy change as a result of the evidence contained in this review?
ASSESSING THE VALIDITY OF TRIAL METHODOLOGY

FOCUSED RESEARCH QUESTION

Like all research reports, the authors should clearly state the research question at the outset. The research question should include the relevant population or patient groups being studied, the intervention of interest, any comparators (where relevant), and the outcomes of interest. Keywords from the research question and their synonyms are usually used to identify studies for inclusion in the review.

TYPES OF STUDIES INCLUDED IN THE REVIEW

The validity of a systematic review or meta-analysis depends heavily on the validity of the studies included. The authors should explicitly state the type of studies they have included in their review, and readers of such reports should decide whether the included studies have the appropriate study design to answer the clinical question. In a recent systematic review which determined the effects of glutamine supplementation on morbidity and weight gain in preterm babies the investigators based their review only on RCTs.

SEARCH STRATEGY USED TO IDENTIFY RELEVANT ARTICLES

There is evidence that single electronic database searches lack sensitivity and relevant articles may be missed if only one database is searched. Dickersin et al showed that only 30–80% of all known published RCTs were identifiable using MEDLINE. Even if relevant records are in a database, it can be difficult to retrieve them easily. A comprehensive search is therefore important, not only for ensuring that as many studies as possible are identified but also to minimise selection bias for those that are found. Relying exclusively on one database may retrieve a set of studies that are unrepresentative of all studies that would have been identified through a comprehensive search of multiple sources.

Therefore, in order to retrieve all relevant studies on a topic, several different sources should be searched to identify relevant studies (published and unpublished), and the search strategy should not be limited to the English language. The aim of an extensive search is to avoid the problem of publication bias which occurs when trials with statistically significant results are more likely to be published and cited, and are preferentially published in English language journals and those indexed in Medline.

In the systematic review referred to above, which examined the effects of glutamine supplementation on morbidity and weight gain in preterm babies, the authors searched the Cochrane controlled trials register, Medline, and Embase, and they also hand searched selected journals, cross referencing where necessary from other publications.

QUALITY ASSESSMENT OF INCLUDED TRIALS

The reviewers should state a predetermined method for assessing the eligibility and quality of the studies included. At least two reviewers should independently assess the quality of the included studies to minimise the risk of selection bias. There is evidence that using at least two reviewers has an important effect on reducing the possibility that relevant reports will be discarded. Pooling results and heterogeneity

If the results of the individual studies were pooled in a meta-analysis, it is important to determine
whether it was reasonable to do so. A clinical judgment should be made about whether it was reasonable for the studies to be combined based on whether the individual trials differed considerably in populations studied, interventions and comparisons used, or outcomes measured.

The statistical validity of combining the results of the various trials should be assessed by looking for homogeneity of the outcomes from the various trials. In other words, there should be some consistency in the results of the included trials. One way of doing this is to inspect the graphical display of results of the individual studies (forest plot, see above) looking for similarities in the direction of the results. When the results differ greatly in their direction—that is, if there is significant heterogeneity—then it may not be wise for the results to be pooled. Some articles may also report a statistical test for heterogeneity, but it should be noted that the statistical power of many meta-analyses is usually too low to allow the detection of heterogeneity based on statistical tests. If a study finds significant heterogeneity among reports, the authors should attempt to offer explanations for potential sources of the heterogeneity.

**MAGNITUDE OF THE TREATMENT EFFECT**

Common measures used to report the results of meta-analyses include the odds ratio, relative risk, and mean differences. If the outcome is binary (for example, disease v no disease, remission v no remission), odds ratios or relative risks are used. If the outcome is continuous (for example, blood pressure measurement), mean differences may be used.

**ODDS RATIOS AND RELATIVE RISKS**

**ODDS AND ODDS RATIO**

The odds for a group is defined as the number of patients in the group who achieve the stated end point divided by the number of patients who do not. For example, the odds of acne resolution during treatment with an antibiotic in a group of 10 patients may be 6 to 4 (6 with resolution of acne divided by 4 without = 1.5); in a control group the odds may be 3 to 7 (0.43). The odds ratio, as the name implies, is a ratio of two odds. It is simply defined as the ratio of the odds of the treatment group to the odds of the control group. In our example, the odds ratio of treatment to control group would be 3.5 (1.5 divided by 0.43).

**RISK AND RELATIVE RISK**

Risk, as opposed to odds, is calculated as the number of patients in the group who achieve the stated end point divided by the total number of patients in the group. Risk ratio or relative risk is a ratio of two “risks”. In the example above the risks would be 6 in 10 in the treatment group (6 divided by 10 = 0.6) and 3 in 10 in the control group (0.3), giving a risk ratio, or relative risk of 2 (0.6 divided by 0.3). Interpretation of odds ratios and relative risk

An odds ratio or relative risk greater than 1 indicates increased likelihood of the stated outcome being achieved in the treatment group. If the odds ratio or relative risk is less than 1, there is a decreased likelihood in the treatment group. A ratio of 1 indicates no difference—that is, the outcome is just as likely to occur in the treatment group as it is in the control group.11 As in all estimates of treatment effect, odds ratios or relative risks reported in meta-analysis should be accompanied by confidence intervals.

Readers should understand that the odds ratio will be close to the relative risk if the end point occurs
relatively infrequently, say in less than 20%. If the outcome is more common, then the odds ratio will considerably overestimate the relative risk. The advantages and disadvantages of odds ratios versus relative risks in the reporting of the results of meta-analysis have been reviewed elsewhere.

Precision of the treatment effect: confidence intervals

As stated earlier, confidence intervals should accompany estimates of treatment effects. I discussed the concept of confidence intervals in the second article of the series. Ninety five per cent confidence intervals are commonly reported, but other intervals such as 90% or 99% are also sometimes used. The 95% CI of an estimate (for example, of odds ratios or relative risks) will be the range within which we are 95% certain that the true population treatment effect will lie. The width of a confidence interval indicates the precision of the estimate. The wider the interval, the less the precision. A very long interval makes us less sure about the accuracy of a study in predicting the true size of the effect. If the confidence interval for relative risk or odds ratio for an estimate includes 1, then we have been unable to demonstrate a statistically significant difference between the groups being compared; if it does not include 1, then we say that there is a statistically significant difference.

APPLICABILITY OF RESULTS TO PATIENTS

Health care professionals should always make judgments about whether the results of a particular study are applicable to their own patient or group of patients. Some of the issues that one need to consider before deciding whether to incorporate a particular piece of research evidence into clinical practice were discussed in the second article of the series. These include similarity of study population to your population, benefit v harm, patient’s preferences, availability, and costs.

STRENGTHS AND WEAKNESSES

While systematic reviews are regarded as the strongest form of medical evidence, a review of 300 studies found that not all systematic reviews were equally reliable, and that their reporting can be improved by a universally agreed upon set of standards and guidelines.

A further study by the same group found that of 100 systematic reviews monitored, 7% needed updating at the time of publication, another 4% within a year, and another 11% within 2 years; this figure was higher in rapidly-changing fields of medicine, especially cardiovascular medicine. A 2003 study suggested that extending searches beyond major databases, perhaps into gray literature, would increase the effectiveness of reviews.

Systematic reviews are increasingly prevalent in other fields, such as international development research. Subsequently, a number of donors – most notably the UK Department for International Development (DFID) and AusAid – are focusing more attention and resources on testing the appropriateness of systematic reviews in assessing the impacts of development and humanitarian interventions.

CONCLUSION

Systematic reviews apply scientific strategies to provide in an explicit fashion a summary of all studies addressing a specific question, thereby allowing an account to be taken of the whole range of relevant findings on a particular topic. Meta-analysis, which may accompany a systematic review, can increase
power and precision of estimates of treatment effects. People working in the field of paediatrics and child health should understand the fundamental principles of systematic reviews and meta-analyses, including the ability to apply critical appraisal not only to the methodologies of review articles, but also to the applicability of the results to their own patients.

REFERENCES

Serological Analysis to delineate between Gastric atrophy and a normal Health stomach without endoscopy

A Case Study By Stephen Joseph Atta Mensah, Ghana

(B.Sc Biochemistry, M.Sc in Clinical Research Student of Texila American University)

Email:- profhenson@yahoo.com

SOURCE


INTRODUCTION

The article "Serological Assessment of Samples from Patients Complaining of Dyspepsia" by Dr. Stephen Mortlock is current article published in the Journal of Gastrointestinal and Digestive Systems in October 2013. This review analyses the article's structure, authority, currency, stability, objectivity and its relevance to students and the health care industry. The review first summarize the article. it then analysis the structure of the article, taking into consideration the concept, methodology of the research, its accessible and the technical flow of the article. The review will also critique the article on the basis of its authority, currency, accuracy, objectivity and its stability. The relevance of the article to in the academia and healthcare industry will also be analyzed in the review. The review will analyze all the relevant data and information (including diagrams) provided by the article before judging on the credibility and the reliability of the article. In entirety, the article is very well written, well structured, clear and relevant in to first year medical students and general practitioners.

KEYWORDS

Patients, Dyspepsia, Healthcare Industry, Medical Research, Digestive System, Gastrointestinal, Heartburns, Abdomen

ARTICLE SUMMARY

The article is a medical research findings in the field of Gastrointestinal and Digestive System. It investigates into the gastrointestinal symptoms such heartburns and discomfort in abdomen which is medical termed "Dyspepsia". The author describes an innovative and renowned method used to
investigate into this condition. The author takes the reader through the detail procedures of the GastroPanel assays in diagnosing "Dyspepsia" in patients. The article explains the findings of the medicals research emphasizing on the sensitivity, accuracy and dependable of the GastroPanals assays in diagnosing "Dyspepsia" due to Helicobacteria pylori and other abnormalities. The article concludes on the notice of encouraging primary health care practitioners to that the serological assessment method of diagnosis is simple, non-invasive, quick and cost effective of diagnosing gastrointestinal disorders compared to the invasive and time demanding gastroscopy or endoscopy.

ARTICLE STRUCTURE

The article opens with an abstract which provide background on which the article was developed. The abstract is also a summary of the article and hence provides an overview and the main objective of the article. The aim of the medical research is stated after the abstract. The aim is very precise, clear and direct to the point. The main body of the article is organized into four headings with varying number and length of paragraphs. Each heading is thoroughly explored with the relevant information and presentations. The pictorially presentations and data enhance the discussion and provides the reader a clear understanding of the article.

The author explored both the strength and limitation of his research at the conclusion or gastric summary section of the article. This shows how objective and realistic the article is. The article also ends clearly stating his position about the use of GastroPanel assays and Gastroscopy in diagnosing "Dyspepsia". The author in his conclusion calls for a further research into the field, which is a good recommendation. The article is a PDF document which makes it easily accessible. References are cited in-text and set out clearly in literature cited section. The article provides links to the journal, contact mail address and the institution of the author and references which allows the reader to evaluate the article’s authenticity, reliability and effectiveness. The article is logically written and structure and is easy for first year medical students, general practitioners and generally reader to understand.

ARTICLE CRITIQUE

AUTHORITY

The article "Serological Assessment of Samples from Patients Complaining of Dyspepsia" by Dr. Mortlock S., is a medical research findings submitted in June 18, 2013 and published in October 30, 2013 in the Journal of Gastrointestinal and Digestive Systems. This journal is a worldly known and accepted journal. Its credible is unquestionable, it is a reliable source of information in the field of medicine. The author, is a researcher at Department of Molecular Biology and a Global Infectious Disease and Microbiology Laison at Quest Diagnostics, Cranford Lane, Heston, UK.. This information tells the credibility of the author and hence the article. The address for correspondence is also provided. This also indicates the credibility of the article. The article provides links to the journal and states the references both in-text and at the reference section. These which upon investigation are correct and reliable. Hence the article is credible and reliable.
ACCURACY

The sources of information in the articles are from current research project publications and articles. The sources of the information in the article are accurate and both the in-text citation and the reference list at the reference section are accurate. Each in-text cited number correspondence accurately to the list. All the information provided in the article is supported by accurate facts and figures and this confirms the accuracy of the article. The strict editorial, referencing and the reviewing processes that the article was taken through contribute to it accuracy. The article provides the link: http://dx.doi.org/.10.4172/216-069X.1000145 which upon checking also confirms the accuracy and the credibility of the article.

CURRENCY

The article was submitted in June 18, 2013 and was published in October 30, 2013 in the Journal of Gastrointestinal and Digestive Systems. The article is a current article written with information from current research and publications. The sources of the information provided by the article are from current research publications between 1996 and 2012. Apart from the reference from the 1996 publication all the other source of information are within the twenty-first century (2002 to 2012). This means the article is really current. Both the reference cited in text and out text confirms this. Therefore the article is current.

RELEVANCE

The article provides the relevant information on the topic to the reader. This article is of great relevance in to medical students and general practitioners. It is also resource to biomedical scientists, nurses and the general population. The article is simply, well structured and clear to understand. The pictorially presentations and data enhance the discussion and provides the reader a clearer understanding of the article. Overall the article is relevant in the academia for medical students and the healthcare industry for general practitioners, biomedical scientist and nurses.

OBJECTIVITY

The article is very objective and unbiased. The article explored three GastroPanel assays in it investigation into diagnosis of "Dyspepsia" Based on the findings, it discussed the benefit and the limitations of the methods used. This article at the conclusion section recommends a further investigation into the topic or condition using different methods. All these shows the unbiased the is. Therefore, the article is objective.
STABILITY

The article is stable. The source of the article and the sources of the information it provides also confirm it. The journal of Gastrointestinal and Digestive Systems is a reliable journal with credible editorial board and publishers. The article is in the PDF format which also makes it easily accessible.

ANALYSIS OF GRAPH

Not applicable

Recent Advance Related to the topic

Not applicable.

CONCLUSION

The article "Serological Assessment of Samples from Patients Complaining of Dyspepsia" by Mortlock 2013, has been critically reviewed. The review summarized the article. Analyse and reviewed the structure, accessibility, credibility, strength, limitation and relevance of the article. The review has also analyzed and critique the article based on the available information. The article is well-structured; it is credible, current, accurate, stable and objective. The credibility of the article is ascertained by the source: J Gastroint Dig. Syst. The article provides the relevant information backed by pictorially figures and diagrams which enhances the readers' understanding. The article is objective and stable. The article is very resourceful and relevant to medical students, general practitioners, biomedical scientists and those in the healthcare industry.

REFERENCES


A BRIEF OVERVIEW OF MAJOR NEGLECTED INFECTIONS OF POVERTY IN EUROPE AS A BASIS FOR FUTURE POLICY RECOMMENDATIONS

Article Review by Mr. Rahul Tulsiram Ingale, UK
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ABSTRACT

Neglected tropical diseases (NTDs), which primarily affect poor people in developing countries, are now being found among the poor in relatively affluent regions as well, particularly in parts of Eastern Europe with a history of war and conflict. To review the prevalence, incidence, and geographic distribution of the major neglected infections of poverty in Europe as a basis for future policy recommendations. The literature from 1999 to 2010 for neglected tropical diseases listed by PLoSNeglected Tropical Diseases) and the geographic regions and countries of (continental) Europe was reviewed. Specifically, areas of conflict in Eastern Europe continue to suffer from the adverse health effects of poverty brought on by weakened economies and disenfranchised populations. People living in the Balkans and the former Soviet bloc countries are most vulnerable to being trapped in a cycle of poverty that is exacerbated by NTDs, particularly ethnic minority groups and immigrants. Among the policy recommendations are increased efforts to determine the prevalence, incidence, and geographic distribution of Europe’s neglected infections, epidemiological studies to understand the ecology and mechanisms of disease transmission, and research and development for new control tools.

KEYWORDS

Neglected infections of poverty; zoonoses, Helminth infections, giardiasis

INTRODUCTION

Neglected tropical diseases are a set of infectious communicable diseases arising from a diverse group of parasitic worms, bacteria, and vector-borne protozoa.[1] The NTDs result in an estimated 534,000 deaths annually [2] and 57 million disability-adjusted life years (DALYs) lost.[3]Given Europe’s recent economic downturn in the setting of approximately 20 years of economic fragility that resulted from war in the Balkans, the fall of communism, and the break-up of the former Soviet Union, it was pointed out that neglected infections of poverty may be highly prevalent in Europe, but especially in
Eastern and Southern Europe and in Turkey, where the living standards are the lowest and the economies remain weak.[4] Here we review the prevalence, incidence, and geographic distribution of Europe’s major neglected infections of poverty and then outline initial steps for formulating health policy recommendations for these conditions.

**BODY**

**Methods**

The literature review was performed for neglected tropical diseases listed by PLoSNeglected Tropical Diseases) and the geographic regions and countries of (continental) Europe. With more than 700 million people, Europe is the third most populous continent (after Asia and Africa), and its roughly 50 states together represent the world’s largest economy. [5] Below table provides the estimated worldwide burden of Neglected Tropical diseases.

<table>
<thead>
<tr>
<th>Neglected Tropical Diseases Worldwide Burden</th>
<th>Disease</th>
<th>DALYs (million)</th>
<th>Deaths/Yr</th>
<th>Global Prevalence (million)</th>
<th>Population at Risk (billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis</td>
<td>4.5</td>
<td>280,000</td>
<td>207</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Hookworm</td>
<td>22.1</td>
<td>65,000</td>
<td>576</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Ascariasis</td>
<td>10.5</td>
<td>60,000</td>
<td>807</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>2.1</td>
<td>51,000</td>
<td>12</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Trypanosomias</td>
<td>1.5</td>
<td>48,000</td>
<td>0.3</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Chagas disease</td>
<td>0.7</td>
<td>14,000</td>
<td>8</td>
<td>0.025</td>
<td></td>
</tr>
</tbody>
</table>
### RESULTS

Among the 27 countries of the European Union (EU), which over-represents the wealthier countries, an estimated 16% of citizens or almost 80 million people live below the poverty threshold, defined as 60% of their country’s median income. Additionally, almost 20% of the EU’s children live in poverty.[6-8]

Poverty in Europe is distributed along a fairly well-defined gradient. Listed in Table 1 is the gross domestic product (GDP) per capita for each European nation (estimated in 2008), organized into four quartiles. Most of the countries in the top two quartiles are Western European nations, while the third and fourth, or poorest quartiles, contain exclusively Eastern European nations. Countries located in Europe’s south eastern region represent the lowest tier.

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Gross domestic product per capita (2008) of European countries, current prices
Some of the countries located in South eastern Europe, including the Balkan nations of Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Kosovo, Macedonia, Montenegro, and Serbia, and Romania, as well as Turkey, are considered Europe's poorest nations and have arguably suffered the greatest devastation over the last two decades.[9] The violence from conflict in this region during the 1990s was considered the worst in Europe since the Second World War, and killed hundreds of thousands of people, while leaving tens of thousands permanently disabled or psychologically devastated, and producing vast numbers of refugees who experienced high rates of malnutrition, communicable diseases, and ectoparasitic infestations (i.e., lice and scabies).[10-11]

The war also destroyed many healthcare and educational systems.[10] A second group of nations made conspicuous by their extreme poverty and disease includes some of the former Soviet bloc countries in Europe, i.e., Belarus, Azerbaijan, Ukraine, Georgia, and Moldova, where the social and health infrastructures were severely affected by the fall of Communism. Both South eastern Europe and the former Soviet bloc countries may have also suffered disproportionately from unemployment and premature deaths from internal violence occurring in the economic downturn and recession of 2008–2009.[12] Specifically, areas of conflict in Eastern Europe continue to suffer from the adverse health effects of poverty brought on by weakened economies and disenfranchised populations. People living
in the Balkans and the former Soviet bloc countries are most vulnerable to being trapped in a cycle of poverty that is exacerbated by NTDs, particularly ethnic minority groups and immigrants. Among the prevalent diseases below was highlighted during research.

- Soil-transmitted helminth infections are commonly found in Turkey due to extreme poverty and poor sanitation; symptoms include severe abdominal pain, malnutrition, and fever. Among children, developmental and cognitive delays have been associated with these infections, leading to decreased school attendance and low wages earned as adults.[13-14]

- In less affluent areas of Eastern Europe, human consumption of beef and fish infected by parasites have increased the prevalence of the food-borne helminthiases. In the same region, the protozoan infection trichomoniasis, a sexually transmitted disease, is severely under-reported.

- Zoonotic bacterial infections, or infections contracted from animals, are of particular concern due to increased animal movement and worker migration from Greece and Turkey. Animal and human migration has led to a re-emergence of diseases that were once under control, as well as outbreaks.[15]

**CONCLUSION**

Efforts are needed to increase research and development efforts for Europe’s neglected infections. Better diagnostic methods are needed to detect these infections in humans and to detect parasites and bacteria in slaughtered animals and in foods. New control tools are also required, including animal vaccines to interrupt the transmission of zoonoses to humans, and human vaccines for many of the helminth infections, and the bacterial zoonoses and arboviral infections described here.

**REFERENCES**


COGNITIVE BEHAVIORAL THERAPY-AN ALTERNATIVE THERAPY TO OVERCOME DEPRESSION IN PATIENTS WITH MULTIPLE SCLEROSIS

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SOURCE

KEYWORDS
Multiple Sclerosis, Depression, Cognitive Behavioural, Researches, Molecular Genetics, Pathophysiology

INTRODUCTION
This review would critically review the article, “Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: a systematic review and meta-analysis”, published in BMC Psychiatry. The review would introduce the article with a brief summary on the basis of available literature and further critique the overall structure of the article. The review would provide information on the accessibility of the article and highlights on current activities that are ongoing in the area of research. In addition, it would also provide information on the article by critically evaluating it on the basis of accuracy, relevance, stability, objectivity and ultimately the credibility of the article set to be reviewed. The cited references would also be critiqued on the basis of the authenticity of the article and presentation of references for future citations.
REVIEW OF LITERATURE

Multiple Sclerosis (MS) is a progressive neurological, autoimmune condition, which affects the myelin sheath within the central nervous system, leading to less effective communication between neurons. Thus, showing symptoms of MS which are experienced early on in the form of muscle spasm, tingling pain in extremities, general weakness and blurred vision. (7) Depression in MS is another most common psychiatric disorders and proposed early care will help maintain the quality of life and prevent suicidal tendencies. (14) It has been proven that the suicidal tendency is 7.5 times higher in MS patients than in general population. (10) The main reasons for depression in MS are the associated physical and cognitive impairments, mood tendencies, treatment side effects of Interferon B and immune system dysfunction. (14) It has also been found that cognitive impairment is generally aggravated when depression is in the moderate to severe range (13).

Depression in MS can be treated by psychotherapy and this has been one of the most acknowledged treatments for the past 3 decades. There have been group cognitive behavioural therapy and Individual Cognitive behavioural therapy (CBT) used to treat depression in the past. Both the therapies have been shown to decrease levels of depression in MS patients and hence, are the best tools for effective management of depression in MS (14). Pharmacotherapy along with psychotherapy have proven to be fruitful however, it has been seen that a structured system which includes regular follow up, monitoring of patient adherence to therapy need to be implemented in patient care for depression in MS (14).

ARTICLE SUMMARY

Depression being a common symptom amongst people with MS; the study primarily aimed to denote the impact of cognitive behavioural therapy in treatment of depression in people with MS. Thus based on the available evidence, a systematic review was undertaken to meet the study objectives. The publications that were subject to review was identified using MEDLINE, PsycINFO and the Cochrane Central Register of Controlled Trials which majorly involved data on individual, group CBT, conducted face-to-face or remotely, to no CBT. Out of 153 studies 7 were identified to review the compounding factors which involved data retrieval for 433 subjects that fulfilled the eligibility criteria of MS with depression and associated psychotic disabilities. The researchers then analysed the collated data statistically to evaluate the impact of CBT on depression and further facilitated with favourable results. Despite the study being a success it had its own limitations as the scope of the study was too narrow to be having a firm conclusion on the research topic. The article therefore concluded on the basis of evidence based medicine that CBT can be an effective alternative in treating the associated depression in MS patients and further improving quality of life. The article may also represent an opportunity for future research in MS. (6)
ARTICLE STRUCTURE

The article was structured very systematically defining every section of the article in an organized manner. The article was separated from the abstract making it distinct in the beginning of the article. The abstract provided highlights of the article under 4 major headings of background, methods, results and conclusion. The author introduced the articles as per the main headings mentioned in the abstract followed by subsequent sub-headings which explains every aspect of the study in a systematic manner. A thorough discussion was provided after the results section and it discussed every aspect of the objective to achieve the endpoint. Limitations to the study were also discussed. Author specific activities too were clearly mentioned under the heading of author’s contribution. The author has also acknowledged the stake holders involved in the success of the study completion.

The articles used as a reference in support to the article are mostly original article and have presented in as per the journals requirement. Author specific referencing was maintained uniformly all across the article. A blend of small and large paragraphs was sectioned under respective headings. The article involved multiple tabular formats, images and graphical representations that were easy to assess and link to the discussion in the article to discuss the outcomes of the research. The article was retrieved from Biomed Central open access in a PDF document format, thus the internal links were not easily accessible. Prior to conclusion the article mentions the necessity for conduct of research in the particular domain and thus influences future research.

ARTICLE CRITIQUE

Authority

The article was published in the BMC Psychiatry. The Journal is an open access journal used for publishing articles which mainly focuses on the information that is obtained in the field of psychiatry either from clinical trials or various observational / behavioural studies thus supporting evidence based medicine. The journal is being supported by Biomed Central Ltd.

The author is currently being involved in multiple researches involving multiple sclerosis population to understand the probable challenges that could be faced in improving the quality of life of patients with multiple sclerosis and also provide alternatives to improve management of the disease with alternative therapies. The article has been verified and approved by all the co-authors and two of the authors involved have shown competing interest. No specific funding was provided for the conduct of the research; however start-up activities were looked up by the lead author.

Accuracy

The article was published in an open access, academic oriented journal specifically for studies or researches involving geriatric population which is majorly supported by the Biomed Central Ltd. The articles published in this journal mainly focuses on researches focused on prevention, diagnosis and
management of psychiatric disorders, as well as related molecular genetics, pathophysiology, and epidemiology. (9) The article was reviewed by all the authors and further peer review by the journal editors along with its acceptance in the journal affirms the accuracy of the article. There were no conflicts of interest observed amongst the authors, however competing interest was observed between Hind and Cooper as they were trialists in the CBT Software for the treatment of depression in people with MS. (6) Further acceptance of the author for scope of bias due to limitations in the study design assures the article can be considered genuine and acceptable for further research.

Currency

The article was published in the journal on January 2014 and was received by the reviewing committee in July 2013. The dates itself indicates the currency of the article as not much success is being obtained in research on MS population. Thus the article may be considered as current.

Relevance

The article was derived from an academic oriented open access journal BMC Psychiatry. The journal is specifically for health and healthcare of psychiatric population irrespective of age and gender, including the effects of healthcare systems and policies. The article would majorly benefit researchers involved in psychiatric research specifically involving MS patients. It would also benefit researchers to further design clinical trials by overcoming the most probable shortfalls.

Objectivity

The article aimed to determine the importance of cognitive behavioural therapy in the treatment of depression in MS patients also provide alternatives; strategies and future recommendation for further research which would enable reach the study endpoints. The article had limitations which the author identified as the study progressed, thus meeting the endpoints of the study were challenging. At the end of the article the author did mention the drawbacks of the study and also acknowledged the scope of bias because of the limitations in the study design. Competing interest is being observed amongst the lead authors of the article. They also acknowledged the work done by each fellow researcher.

Stability

The article has been published in a recognised open access journal wherein articles go through a strict review process and thus is considered to be stable and resourceful for researchers.

Analysis of Graph / Image / Table

The research article involved graphs, images and tables. Study specificities were discussed systematically which clearly defined every aspect of the expected outcome. The graphs were analysed statistically and discussed effectively with proper referencing throughout the article.
RECENT ADVANCE RELATED TO THE TOPIC

MS is an autoimmune disease that affects an individual making him incompetent in dealing with certain activities of life. Associated complication in the form of depression, mental and physical impairment does influence the quality of life of such individuals. It is thus that researchers are working on implementing newer techniques and/or therapy patterns to overcome the clinical condition thus improving quality of life of these patients.

Researchers are currently involved in generating data on the basis of available data to provide future researchers scope for further research. In the past, studies have explored age-related patterns of disease presentation, treatment approaches, survivorship, quality of life, impact of co morbidities, and functional outcomes which indirectly may help researchers to generate hypothesis in overcoming the clinical condition. (5) In addition to the two treatment methodologies listed above complementary and alternative medicine (CAM) is also useful to help manage the different lifestyle changes and stress brought upon by the disease (10). CAM involves a wide range of disciplines and traditions from all across the horizon. These help to provide holistic healing to the patients as it encompasses not only diet and exercise but also stress management strategies. (10) For those patients who do not respond to the therapies mentioned earlier in the literature review section, the following three methodologies may be adopted: trans cranial magnetic stimulation, which is under study at present, Vagus nerve stimulation, which has been used in since the late 1990s in epileptic patients and electroconvulsive therapy (ECT), however, ECT may have negative impacts on the blood brain barrier and hence, the patients need to reassess the risks vs benefits before undergoing this procedure (12). In addition, cognitive and behavioural treatments mainly aiming to psychoanalytic therapies, systematic therapies, integrative therapies and methodological integrations of cognitive, behavioural and humanistic approaches are widely practised. (15). All these additional therapies are subject to further research.

CONCLUSION

The article published by Daniel Hind has been reviewed critically on the basis of its authority, accuracy, relevance, stability, currency and objectivity. The article was presented in a systematic manner defining each and every section as mentioned in the abstract. The article involved tables, diagrams and graphical representations which were effectively discussed and referenced throughout the study. The study was published in an academic journal which was supported by Biomed Central Pvt. Ltd which affirms the authenticity of the article.

MS is an autoimmune, neurological disorder that impacts the life of patients drastically making them highly dependent on their peers. Associated depression aggravates the clinical condition making it difficult for the patient to undergo his daily activity due to the mental and physical impairment involved. Various treatment suggestions in the form of psychotherapy, CBT along with CAM therapies are being practiced and are in research to delve the best practise and make it available.

The study aimed to determine the impact of CBT on treating depression in MS patient’s on the basis of a systematic review which was satisfactorily attained by the author. A scope for bias too was
highlighted in the discussion under the limitation in the study. The currency of the article suggests further scope for research in understanding the commonly faced challenges and making an effort to overcome them. Currently there are studies that are ongoing to denote improvement in care that could be provided to the MS patients in all aspect of treatment, management and palliative care.

REFERENCES


BRAIN TUMORS – THE ROLE OF MONOCLONAL ANTIBODIES THERAPY AND CHALLENGES OF BLOOD BRAIN BARRIERS

Article Review by Dr. Kanthimathi Kumaraswamy, India
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SOURCE

KEYWORD
Neuro Oncology, blood-brain barrier, Monoclonal antibodies, Breast Cancer, Brain tumor, Refinement

INTRODUCTION
This review critically reviews the article monoclonal antibodies therapy in neuro oncology The Brain tumors In applying mAb therapy to brain tumors, both expectations and interpretation are seems difficult due to blood-brain barrier (BBB). It prevents the antibodies from entry into the brain but in case of brain tumors their entry is more complex. Brain tumors (the target), antibodies (the magic), how antibodies attack tumor (the bullet) and how they reach it (through blood brain barrier) are reviewed. With this as introduction, practical experience with mAbs for brain tumor targets is by Clinical experience with mAbs in brain tumor therapy indicates that it is less inherently toxic than the conventional therapies and far safer for widespread delivery

Three of the best-studied antibody/target combinations Bevacizumab and GBM. It hard to define the effect of the antibody itself on tumor growth bevacizumab primarily reduces edema. Other questions concern response criteria. How to weigh overall survival as opposed to progression-free survival; Rituximab and PCNSL. Rituximab targets the common B-cell marker CD20 PCNSL, which is typically a B-cell lymphoma. Trastuzumab and metastatic breast cancer Monoclonal antibodies (mAbs) serve as tumor-specific magic bullets in two ways. As bullets, they would move through the blood to reach and
attack tumor targets and specificity of a single antibody would provide the magic, breast cancer patients respond to systemic mAb treatment, but then metastases appear in the brain. Limitations of clinical trials and drawbacks of pre-clinical models interpretation of clinical results difficult - increase in overall or progression-free survival, or simply an improved quality of life, are certainly of benefit to brain tumor patients- delivery strategies and tumor sites

ARTICLE SUMMARY

This article relates to the use of monoclonal antibodies in neuro oncology this therapy is widely used in many cancers (breast, colorectal, B-cell Lymphoma) but in brain tumors the efficacy the role of blood brain barrier is a special concern. The success against the brain tumors depends on getting past the blood brain barrier to better attack the brain tumor targets. The properties of monoclonal antibodies are-it is highly antibody specific. Of special relevance for antibody therapeutics, FcRn, the Fc receptor that protects antibodies from degradation in serum, is highly expressed on brain vessels. Specific relevance for brain tumor, radiotherapy is thought to alter the BBB in ways that increase antibody access to tumor sites.

Clinical experience reveals with Three Brain Tumor/Antibody Pairs Bevacizumab and GBM. Rituximab and PCNSL Trastuzumab and brain metastasis of breast cancer, the median survival after therapy for GBM lasts for only 15 months or lesser and the concentration of the drug is measurable in CSF and not at the tumor sites, hence the Need for new therapies, In the brain, is of paramount important. What allows entry through blood brain barrier entry of substances from the blood, through BBB is effective at selectively permitting entry of necessary Active transporters that import nutrients and regulatory molecules.

One approach is exploit these transporters. Of special relevance for antibody therapeutics, FcRn, the Fc receptor that protects antibodies from degradation in serum, is highly expressed on brain vessels FcRn-mediated transport is bi-directional, and the predominant direction can be modified experimentally. Whether FcRn might also act to bring antibody into brain tumor sites?

The BBB along with various stage of brain tumors are depicted with two models. The complexity of tumor therapy, difficulty of direct local measurements, limitations of clinical trials and drawbacks of pre-clinical models all complicate interpretation of clinical results. The goals for the future are, as for all tumors, to increase the benefit and reduce the cost of the therapeutics

For the brain, where delivery to micro-tumor is a great challenge, clearer understanding of the nature and role of the BBB, complemented by improved methods for opening or bypassing it is another goal to be accomplished. Summarizing the question that lay ahead is how mAbs can be used effectively in brain tumors whether it depends on antibody itself, a fragment or a synthetic alternative; how the agent will be delivered passively or actively through BBB into the brain
REVIEW LITERATURE

HER-2/neu status is critical, and careful cardiac monitoring is warranted because of cardiac toxicity of trastuzumab in the treatment of her-2-positive early breast cancer (1-4) Rituximab in lymphoma A polymorphism in the complement component C1qA correlates with prolonged response following rituximab therapy of follicular lymphoma (5-6)


ARTICLE STRUCTURE

This article relating to monoclonal antibody therapy in cancer in neuro oncology limitations caused by BBB is a concern .The rationale of this article is to rethink with the findings of Clinical experience which indicates that mAbs is less inherently toxic than the conventional therapies and safer for widespread delivery , is likely to increase in overall or progression-free survival and an improved quality of life.

These are certainly of benefit to brain tumor patients if delivery strategies are manipulated and tumor sites targeted. The sub headings target, magic and bullet is aptly said target are tumors in the brain antibodies (mAbs) would serve as tumor-specific magic bullets in two ways. As bullets, they would
move through the blood to reach and attack specific tumor targets. The specificity of a single antibody provides the magic, new insights are still needed for tumor in the brain. The 3 types of Brain tumors – 1] Glioma - primary brain tumors arising within the brain, the high grade glioblastoma multiforme (GBM), most common in adults. 2] primary central nervous system lymphoma occurs in two very different contexts: in patients with AIDS or other forms of immunosuppressed patients. 3] Metastatic. Blood-borne metastases from other organs are more frequent than primary brain tumors; mostly from tumors of the lung and breast. The Bullet: Antibodies can lead to death or arrest of a tumor target, it directly blocks activity of a target molecule by binding to it, others are s of Fc receptors binding. More recently another FcRn receptor, binds to an antibody to protect it from degradation. This leads to the prolonged serum half-life of an antibody

In brain tumor, radiotherapy is thought to alter the BBB in ways that increase antibody access to tumor sites. The entry of mAbs is restricted by BBB in micro brain tumors but as the size of tumor increases the properties change, Success against brain tumors needs passing of mabs through BBB

ARTICLE CRITIQUE

Authority

The author has published related articles in PUB MED online. He tries to find ways to improve monoclonal antibody therapy in Brain tumor as it is less toxic with a view to improve the quality of life and at the same time prevent progression of tumor. The credibility to the author goes with his intent research strategies aiming multiple points of approach.

Accuracy:

The source of the information in the article is a current research. It was also backed up and supported by Clinical findings, recent reference list with these sources cited in-text to support both the literature review and the research itself. The natural evolution of mAb therapy for any tumor at any site is towards redundancy and refinement. Redundancy, is alternative targets are identified and alternative antibodies are prepared against promising targets, old or new. Refinement is that the new antibodies can be designed to solve specific problems: to avoid known cross-reactions or to work by means of alternative effectors mechanisms

Currency:

The journal was published on line in March 1 2011, The research it describes was current and the article cites up-to-date references in the text (ranging from 1996-2009). Therefore the article is current. The article includes 74 referenced articles involving areas connected to the subject of this article concerned. It compromises 2 Meta analysis, one systematic review and other related articles Vaccines for lymphomas: idiotypic vaccines article by Houot R, Levy R. Recent advances in blood-brain barrier
disruption as a CNS delivery strategy by Bellavance MA, Blanchette M, Fortin D are some examples of PUB Med which the author has referenced

**Relevance:**

This was a Research database, which has high credibility in future research context. It was written to inform researchers rather than to entertain or advertise. There is evidence that systemic mAb treatment can benefit patients with brain tumors or other CNS pathology. The nature and site of antibody activity are less clear and It would be relevant to this group for future research The extent to which antibody enters and acts at tumor sites within the brain itself, tumor within the brain, systemic delivery of mAbs is especially relevant. The focus has been on the role of the BBB, to interpret findings for a variety of delivery strategies and tumor sites.

**Objectivity:**

The information of monoclonal antibody therapy in brain tumor is objectively developed, well supported with a current Clinical findings about the efficacy in various brain tumors research and all evidence are acknowledged and referenced.. The article acknowledged the complexity of the issues discussed in a number of ways. For example, Complex structure and resistance of molecules through Blood brain barrier and supported their research decisions with references to the appropriate and relevant literature. The way the article dealt with the three words bullet magic and target was really superb

**Stability:**

The article, with its source PMC on line Publication is stable as a resource. Improved clinical trial design will be important for all brain tumors, and supported by more predictive pre-clinical models

**ANALYSIS OF GRAPH/IMAGE/TABLE**

*Table 1* -Tumor/antibody combinations emphasized in the text

*Figure 1*-Two patterns of tumor growth in the brain. Tumor often grows around blood vessels (left), but some tumors can also infiltrate the brain parenchyma (right).

*Figure 2* Distribution of tumor antigens. A tumor cell displays a characteristic combination of components, many of which are also expressed by normal cells. Even though they may not be unique to the tumor, shared antigens can serve as practical tumor targets.

*Figure 3* A varied role for the BBB. Possible relationships among tumor (black circles), gadolinium (Gd, black dots), antibody (AB, Y shapes), blood vessels (grey) and the blood-brain barrier (BBB), under different conditions of tumor growth are depicted.

*Figure 3 A- 3F* relates to different types of models depicting the mAbs and blood brain barrier possibility of acting in brain tumors
RECENT ADVANCES RELATED TO THE TOPIC

Nicholas Butowski, MD, and Susan M. Chang, MD

The large molecular weight of antibodies is likely to result in inefficient drug delivery into the brain because the blood-brain barrier prevents their passage into brain parenchyma. For this reason, mAb therapy is often delivered intra tumorally rather than systemically. Such intra tumoral delivery is generally done via catheter or convection-enhanced delivery methods and might avoid systemic targeting and toxicity. It can be performed into the tumor itself or after resection. In an effort to increase effectiveness, mAbs may be conjugated with drugs, toxins, or radioisotopes. And much is left to discover.

Recent advances in molecular and cell biology have led to a greater understanding of molecular alterations in brain tumors. These advances are being translated into new therapies that will hopefully improve the prognosis for patients with brain tumors. Brain tumors commonly express molecular abnormalities. These alterations can lead to the activation of cell pathways involved in cell proliferation. This knowledge has led to interest in novel anti-brain-tumor therapies targeting key components of these pathways.

Many drugs and monoclonal antibodies have been developed that modulate these pathways and are in various stages of testing. The use of targeted therapies against brain tumors promises to improve the prognosis for patients with brain tumors. However, as the molecular pathogenesis of brain tumors has not been linked to a single genetic defect or target, molecular agents may need to be used in combinations or in tandem with cytotoxic agents. Improved clinical trial design will be important for all tumors, refine the specificity and modifications of the antibody molecule itself. Synthesize novel agents, using knowledge of antibody structure and function as a guide.

CONCLUSION

Monoclonal antibody therapy in brain tumors, being less toxic, highly specific and cost effective will certainly be of benefit to people suffering from brain tumors, it would not only prevent progression of disease progress but at the same time will increase the quality of life of the patient. The major challenge is the blood brain barrier which does not allow mAbs to cross through it hence a complementary evolution of understanding and technology is needed to improve delivery of therapeutics to tumor masses.

A better understanding of the nature and role of the BBB, complemented by improved methods for opening or bypassing it is necessary and interpreting variety of delivery strategies at tumor sites. In the brain, interpretation of antibody levels is by taking local measurements in cerebrospinal fluid (CSF). This does not take into account anatomic distribution of the antibodies and limitations of clinical trials and drawbacks of pre-clinical models all complicate interpretation of clinical results.
Two parallel approaches for mAbs therapy - One is to refine the specificity and modifications of the antibody molecule itself. The other is synthesize novel agents with the details of antibody structure and function as a guide. The whole antibody molecule has great value. It has a long half-life and can mediate multiple functions, with new functions and uses that needs to be studied. Still the key mechanisms used by the most successful antibodies in human patients are yet to be established.

**REFERENCE**


STRATEGY OF CONTEXTUAL BEHAVIORAL SCIENCE

Article Review by Mr. Praneeth Kamarapu, India
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SOURCE


KEYWORDS

Contextual behavioural science, Behavioural Psychology, Behavioural Medicine, epistemology, ontology, health intervention

INTRODUCTION

This review critically reviews the article ‘Contextual Behavioral Science: Creating a science more adequate to the challenge of the human condition’ in the journal Science Direct Journal. The review will first summarise the article. Secondly, it will briefly analyse the effectiveness of the article’s structure, investigating how the information is set out and whether the reader can access it efficiently. Thirdly, the review will critique the article, evaluating its authority, currency, accuracy. Overall the article was well written, clear and relevant.

ARTICLE SUMMARY

The purpose of the article is to include physicians, social workers, nurses, midwives, and community healthcare workers working with vulnerable populations, Behavioural medicine practitioners. Behavioral medicine is at the intersection of three practice models familiar to practitioners in developing countries, namely:
i) The Medical Model,  
ii) The Traditional Medicine Model and  
iii) The Public Health Model.

The article provides the goals for nature, scope, and purpose of Contextual Behavioral Science (CBS). Emerging from behavioral psychology but expanding from those roots, CBS is based on contextual assumptions regarding the centrality of situated action, the nature of epistemology versus ontology, and a pragmatic truth criterion linked to the specific goal of predicting-and-influencing psychological events with precision, scope, and depth.

ARTICLE STRUCTURE

The present article describes the nature, scope, and purpose of Contextual Behavioral Science (CBS). Emerging from behavioral psychology but expanding from those roots, CBS is based on contextual assumptions regarding the centrality of situated action, the nature of epistemology versus ontology, and a pragmatic truth criterion linked to the specific goal of predicting-and-influencing psychological events with precision, scope, and depth. These assumptions and goals explain the characteristic features of CBS including its environmentalism, focus on theory and principles, and its reticulated or networked program of theory development, research and practice.

Domains of development include increased linkage to multi-dimensional and multi-level evolution science; development of principles that describe the interaction of behavior and symbolic events with genetic, epigenetic, and cultural dimensions; expansion of theoretical and model development to a broader range of areas of human complexity; advances in measurement theory and practice; the development of techniques and components linked to contextual processes and principles; broad testing of these methods; additional research on mediation and moderation; more concern for effectiveness and training; and enhancement of a diverse development community.

AUTHORITY:

The journal, the Science Direct Journal, is a publication of the American Public Health Association. The author Steven C. Hayes from the Department of Psychology, University of Nevada, Reno, NV 89557-0062, USA.

ACCURACY:

The source of the information in the article was a current research project. It was also backed up and supported by a comprehensive, recent reference list with these sources cited in-text to support both the literature review and the research itself. The strict editorial and refereeing processes also contributed to the article’s accuracy.
CURRENCY:

The journal was published in Oct 2012, while the article was accepted for publication in Sep 2012. The research it describes was current and the article cites up-to-date references in the body of the text. Therefore the article is current.

RELEVANCE:

This was an academic Journal of Contextual Behavioral Science, which has high credibility in a research in public health context. It was written to inform researchers and students rather than to maintain maximum health percentage in public. It would be relevant to groups but particularly any academic interested in community based innovations and in health generally. It could be a difficult article to read and understand. This is an important article to students in department of psychology.

OBJECTIVITY:

The main objective of the article includes CBS is a broad program of research and practical development. CBS is best viewed as part of multi-dimensional and multi-level evolution science. It emerged from behavioral psychology, but stands on its own. Its assumptions explain its environmentalism, focus, and reticulated approach. CBS has scores of important practical and empirical areas for exploration.

CONCLUSION

This review has both summarized and correctly reviewed Steven C. Hayes’s article ‘Contextual Behavioral Science: Creating a science more adequate to the challenge of the human condition’. The content, structure, strengths and limitations of the article were analyzed and reviewed. The article has contributed to the literature in terms of its valuable critique of current research study on psychology and their health issues and the implications provided for both health interventions and future research collaborative possibilities.

REFERENCES


MYCOBACTERIUM TUBERCULOSIS (MTB) DETECTION USING ZIELH-NEELSON (Z-N) STAIN TO IDENTIFY ACID FAST BACILLI

Article review by Ms. Martina Awuor Ouma, Botswana

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SOURCE

Mohammed SS Ansari, Mohammed Hidayath, Waseem Kawoosa, and Arif Ghouse A comparative study of sputum induction in suspected pulmonary tuberculosis, Department of Pulmonary and Critical Care Medicine, Mahavir Hospital and Research Centre, 10-1-1, Mahavir Marg, AC Guards, Hyderabad 500004, Andhra Pradesh, India. Volume 5, pages 83-90, 2013, Indexed by Scopus (Elsevier), Co-Publisher: OMICS Group, www.omicsonline.org.

KEYWORDS:

Tuberculosis, Sputum, Pulmonary induction, Nebulisation, Mahavir Hospital, Acid Fast Bacilli

INTRODUCTION

The review of the article identifies Tuberculosis (TB) as an infectious disease which is known worldwide with reference to India being the second largest populated country in the world. Secondly it identifies Acid Fast Bacilli using Zielh-Neelson (Z-N) staining in a clinical laboratory for the identification of TB using the best possible method to obtain secretions from the lower airways of patients as compared to bacterial identification which is normally used.

Various diagnostic methods and materials used to evaluate the article authority and accuracy will be outlined which includes sample study, period of examination, ethical practices prior starting the study, study protocol, study design, inclusion and exclusion criteria carried out systematically under sterile conditions.
Analysis of AFB smear will be explained and presented using tables which are instrumental in the identification of other diagnostic methods like sputum smear microscopy and X-ray method. Conclusion of the study will be based on the safest method for identification of the organism, which is cost effective and has the potential to offer treatment to the suspected patients. On the other hand, the article has obtained its objectivity and coverage by using various ethical committees and by declaring no conflict of interest among the authors who have contributed equally to the study.

Finally, the evaluation of the article will be carried through the use of well designed and précised questionnaires, a case sheet proforma plus relevant referees attached to the article to aid more understanding.

**REVIEW OF LITERATURE**

**ARTICLE SUMMARY**

The aim of the article review is to carry out a comparative study of sputum induction in suspected pulmonary tuberculosis in India. The recommendation made by WHO in the detection of Acid Fast Bacilli is the initial approach to the diagnosis of TB. A comparison done between three groups, each consisting of forty TB patients has given the article its authority in the identification of the organism among diverse number of people. The estimation of article accuracy has been demonstrated by the use of different study protocol i.e. nebulised levasolbutamol, 0.9% normal saline & 3% hypertonic saline plus a detailed history and thorough clinical examination of the patient.

A well designed questionnaire was used to collect information on respiratory symptoms and to identify patients who are suspected of pulmonary TB. Nebulisation as a collection method was chosen due to its safety on children, postprandial, cost effectiveness and less time consuming.

Depending on hydration level of the patient, samples were collected under sterile conditions. Analysis of sputum was carried out under sterile conditions and to prevent contamination of the sample and materials were sterilized and disinfected over night.

The results were calculated, tabled and ranked in percentages showing the strengths and limitations of the three smear gradings. Sputum induction has been used for studying various diseases and also for the development of standardized procedure which improve the quality and reproducibility of the sputum sample.

**ARTICLE STRUCTURE**

The introduction of the article with an abstract, which is short and précised to the point motivates the reader and makes it easy to understand the entire content of the article within a short period of time.
The justification and importance of the article is well explained in simple scientific terms highlighting the need for the comparative study of sputum.

The article comprises of both long and short paragraphs which captures more details, provides more relevant information and can serve as references of the study. The headings and subheadings did actually reflect the informational content covered and provide a clear practical identification of the findings. The development of the paragraphs are systematic hence provides a flow of information linking paragraphs with the headings, subheadings and the titles and eventually with the conclusion.

The collection of information from reliable primary sources “Mahavir Hospital and Research center, WHO and the Revised National Tuberculosis Control Programme makes the article more reliable. The author also cited relevant information and references from the secondary sources making the article objective in its judgment. The findings were accurate based on the comparison between different solutions, calculated and measured giving fair and actual results.

The conclusion provides various current and future methods for the investigations giving their advantages and limitations. Clearing of the institutional ethics before carrying out the project and declaration of no conflict by the authors contributes to its compliance. Linking the article to different authors and references enable the reader to understand the publication in detail and the provision of the case sheet proforma together with the questionnaire are methods of evaluating the article.

**ARTICLE CRITIQUE**

**AUTHORITY**

The Department of Pulmonary and Critical Care Medicine, Mahavir Hospital and Research Center in Hyderabad, Andhra Pradesh India where the research was conducted is a reputable organization which has been acknowledged for the provision of adequate facilities. The article objectivity is outlined by the declaration of no conflicts of interest by the authors plus the clearance of the institutional ethics committee prior carrying out the research. The author’s equal contributions and support from the World Health Organization (WHO) plus the Revised National Tuberculosis Control programme is accredit to the organization.

**ACCURACY**

The author demonstrated the best accurate methods of obtaining the right results using the latest methods and techniques, for obtaining secretions from the lower airways using the study sample from three groups consisting of forty TB suspected patients within one year duration.

The validation of the committee prior the study is part of quality standard for the publication plus collection of specimen from diverse number of people(gender, age and state condition of the patient) used for analysis.
Despite the entire process being carried out under sterile condition, including labeling, sterilization and disinfection of equipments and materials, the method has low sensitivity and has little value in patients who cannot produce sputum spontaneously.

**CURRENCY**

The article is current since it was published on the 5th August 2013 whereas it was accepted for publication on the 27th July 2013. The current study involves diagnosis of HIV-Seronegative patients using AFB test and induced sputum test using normal saline, hypertonic saline in the chest symptomatic i.e. in young children, postprandial & OPD(out patients procedure departments) procedures with no to minimal adverse effects.

Different examinations being carried out for diagnosis of patients using the latest methods of analysis like the CVS/CNS test for respiratory system. The need of sputum induction to move from the research laboratory to the clinic and Beta2 –Agonists which enhances mucocilliary transport in healthy subjects is useful in improving quality microscopy.

**RELEVANCE**

The informational content of the article is relevant for the current research on TB and HIV related complexes. The aim of the research is for the detection and treatment of estimated TB cases in the community including HIV related cases.

The article explains the best procedure of obtaining secretions from the lower airways of individuals for early diagnosis. It further identified the safest method of collecting sputum from children, postprandial and OPD in a cost effective manner, within the shortest time. The different methods and materials used in sputum induction were compared.

A comparative study was also conducted amongst different age groups, gender and patients showing different signs and symptoms. The use of a case sheet proforma (annexure1) and the questionnaire in the study was designed to allow easy collection of information on respiratory symptoms and identified patients who were suspected of “pulmonary TB” both with dry cough and scanty sputum and this makes the article relevant for the current research work and students who are actually carrying out research on TB as an infectious disease.

**OBJECTIVITY**

WHO recommends the detection of AFB and also point out the benefits and limitations of using such procedures during analysis. The study method consist of three groups of forty TB suspected patients from different diverse groups in terms of age, condition of the patients i.e. those who have taken anti-tuberculosis treatment, other causes like chest pain, cardiac and renal.

Taking consideration of patient hydration level the procedure used in sample collection gives the article its objectivity for example:
First nebulised spot sample
Next day early morning home collection sample and
Second nebulised spot sample

STABILITY

The publication is stable as it describe the process as being advanced and non invasive research tool providing information about inflammatory events in the lower airways and has been used for studying various disease. The development of standardized methods for sputum induction has improved the quality and production of sputum sample however the best possible dose for sputum induction needs to be improved consistently by further studies.

ANALYSIS OF GRAPH / IMAGE / TABLE

(Not applicable)

CONCLUSION

The article has given a comprehensive overview on “a comparative study of sputum induction in suspected pulmonary tuberculosis”. The relationship between the components part of the article is consistent. The informational content of the article is relevant for current research and the language used is simple, understanding and relevant for the scientific research. The scope on which the article was created and used is relevant for health interventions and offer future development in research. The author summarized both advantages and disadvantages of the article and provides the available recommendations for future research.

Contributions from various recognized bodies like the Revised National Tuberculosis Control Programme (RNTCP), the management of Mahavir Hospital and Research Center plus the recommendations from World Health Organization (WHO) provide the authenticity of the article.

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TRANSLATIONAL ERRORS IN THE ARTICLE – ‘PANAX GINSENG C.A MEYER ROOT EXTRACT FOR MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL’

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SOURCE


KEYWORDS

Ginseng extract, COPD, Clinical research translation, CAM, translational research, Complementary and Alternative Medicine

INTRODUCTION

The review will assess the article: ‘Panax ginseng C.A Meyer root extract for moderate Chronic Obstructive Pulmonary Disease (COPD): study protocol for a randomised controlled trial’, published in 2012 by Xue et al. in the E-journal, Trials, volume 12 number 164. The assessment will focus on the knowledge contribution of the article to the field of translational medicine and evidence based research for use of Complementary and Alternative Medicine (CAM).

Translational medicine, a research dissemination tool for advancing gains of basic laboratory discoveries to populations via clinical studies, has come to be a very useful tool for the practice of conventional medicines. This paradigm has also found usefulness as an emerging trend in the development and practice of CAM. CAM, though older than conventional medicine, have found rebirth...
in the healing sphere owing to public demand and based on successful psychometric evaluations using various rigorous study designs of Randomised Controlled Trials (RCT).

The goal of designing a study protocols is to obtain a tool for measuring and evaluating how an intervention, medical device or diagnostic contribute to improvement in health status or knowledge. Hence, this review will assess the scientific rigour and proof of principles demonstrated by the author in developing the study design.

The article will be summarised, assessed on presentation effectiveness and the depth of literature on current knowledge. A critique on authority, currency, relevance, accuracy, objectivity and stability will be carried out and the conclusion will present the statement of scientific value of the article.

**REVIEW OF LITERATURE**

The article cited twenty six (26) literary works in the key subjects of COPD, CAM and properties of panax ginseng. The literature review dwelt largely on the state of COPD disease such as Global Initiative for Chronic Obstructive Lung Disease (GOLD) consensus report, (Rabe, et al. 2007); COPD prevalence and its measurement (Halbert, et al. 2006), issues of early diagnosis in primary care treatment, (Price, et al 2011), etc. Measurement literatures cited dealt with measurement of health-related quality of life (HRQoL), COPD respiratory symptoms (Ferrer, 1997), application of confidence intervals for multiple inference, (Ludbrook, 2000).

Considering that the article was written to present a RCT protocol and in line with the authors desire as stated ‘to guide the future development of quality clinical trials’ protocols on herbal medicine by other investigators’, it would be expected that the authors should have an expanded review of works on protocol development. Works such as Walker and Anderson (1999) and Elder et al. (2006) are examples of protocol literatures relating to CAM studies that provide relevant insight of the research experience of other workers. Added to the cited works of Gross et al. (2002) and others, the emphasis of the literature survey would be on the subject of clinical studies’ protocol developments.

Notwithstanding that the original study could generate several publication outcomes, the content and structure of each publication should be determined from the title. This literature survey failed to objectively focus on aspects that are very relevant to the topic: ‘study protocol for a randomised controlled trial’. The literature review fell short of providing adequate evidence of a rigorous background study necessary for educating readers on one of the articles critical goal of guiding researchers in designing clinical trials of herbal medicines. Readers must thus search other protocol and translational literatures to obtain necessary information to be able to exploit the full value of the article.

**ARTICLE SUMMARY**

The stated objective of the article is to evaluate the safety profile and therapeutic value of a standardised ginseng root extract on symptomatic relief, and focusing on QoL improvements in patient
with moderate COPD. This objective refers to the outcome of the article when applied in a study to evaluate standardised ginseng extract. The article in itself was written to present a protocol designed for an evaluation comparing standardised ginseng extract to placebo. The design is a randomised, double-blinded parallel clinical trial in multi-centres with a placebo-controlled arm.

The authors presented an in-depth review on the prevalence of COPD and its global profile on mortality and morbidity stating that COPD was an emerging healthcare burden with a 10% prevalence and global cause of death projections ranking by 2030 of 3rd. There is no cure for the disease, adverse effect limits use of available treatments, there is a growing interest and use of CAM for its management and ginseno sides from ginseng have been identified as an effective treatment. However, the lack of clinical evidence necessitates designing RCTs to evaluate safety and efficacy of ginseng in COPD.

The protocol design is defined with an objective of four key research questions. The authors elaborately discussed the design methodology under the following headings: Design, Study duration, subjects, inclusion and exclusion criteria, ethical issues, randomisation, sample size, treatment, outcome measures, adverse event reporting, and statistical analysis. A flow chart is used to demonstrate the study activities while a table indicate the time and nature of measurements.

**ARTICLE STRUCTURE**

The article opened with a structured abstract providing an overview of the content of the article under the subheadings of *Background, Aim, Methods and Discussion*. The main body of the article was laid out in four (4) key headings of background, objective, method and discussion.

The background presents a review of issues around the aetiology and prognosis of COPD as a public health challenge and dwelt largely on the state of COPD disease without discussing issues that borders on the core aim of the article which was the description of the design of a randomised, double-blinded, placebo controlled clinical trial. The authors highlighted the medicinal properties of ginseng as a probable treatment option for COPD.

Under the heading objective, the article stated its core objective. This stated objective is at variance with the content of the article. The Unstated objective can be deduced from a statement in the structured abstract under the subheading of Method as ‘to present the protocol of a randomised, double-blinded parallel clinical trial design with a placebo-controlled arm.

The article defined in a very cogent manner how the study hopes to achieve its stated objective by addressing a set of four questions. In defining the methodological approach to the proposed study, the authors described the various steps to be taken in order to obtain and analyse data. Although the authors failed to provide a scholarly background on protocol development, the design presentation was quite articulate and easy to understand and use. A list of abbreviation was provided making the reading of the article easy. The references were unambiguously listed.
ARTICLE CRITIQUE

Authority:

The authors have the necessary professional background and are affiliated to international medical research institutions. Their interdisciplinary background suggests a widened scope of scholarly activity. The registration of the trial in Australia, the funding from three institutions (the National Health and Medical Research Council (NHMRC), the National Institute of Complementary Medicine Australia, and the Guangdong Provincial Academy of Chinese Medical Sciences, China) suggest a robust research evaluation hence a sound authority. Finally the article was published in the Trials. This is a peer-reviewed open access, E-journal encompassing all aspects including randomized controlled trials’ findings and performance. It is included in PubMed. The article is thus considered of an authoritative source.

Accuracy:

The article is not considered very accurate due to the authors’ neglect of relevant literature which is necessary to present an empirical basis for the protocol design. The authors planned to integrate rigorous clinical research methodology of contemporary science to design the protocol and went further to identify ethical principles and guidelines of Helsinki including Good Clinical Practice documents as evidence of their knowledge but failed to cite them. Next, the stated objective was of the outcome of the designed protocol for which the article was written and not that of the article. Lastly, the introductory part of the article discussed the proposed RCT while the later part discussed the protocol development. This imply presentation of two inconclusive papers; one on the study to evaluate the therapeutic value and safety profile of a standardised ginseng root extract and another describing an RCT protocol design. However, the reference listing is accurate.

Currency:

This article was published in 2011 and deals with clinical and translational research issues in CAM. CAM related translational studies are of scholarly demand owing to changing medical strategies. Owing to the few treatment options in COPD, the use of traditional Chinese medicines is considered an attractive opportunity however, there is a dearth of evidence bases for use, hence the need for this type of publications and considering that the protocol will guide other similar studies. The authors cited up to date references in the article and demonstrated current knowledge of principles and guidelines of ethics as it affects development of clinical research protocols.

Relevance:

This article is considered relevant to clinical research translation. This is especially so if we consider the dearth of evidence based studies in complementary and alternative medicines that are gradually becoming the option of choice for many different disease conditions.
The protocol design as presented considered all necessary aspects that will lead to data gathering, analysis and ethical consideration.

It is considered as a scholarly material contributing to knowledge and providing guidance for design of similar studies. It is important though for readers to carefully scrutinise the article and identify areas of relevance as it concern their interest considering the slight mix up in defining the real focus of the article.

**Objectivity:**

The area of core error of this article lies in the lack of objective focus in the writing of the paper. The title as given by the authors suggests that the paper will discuss the subject of developing a study protocol for RCT. However, the paper dwelt largely on the aetiology and prognosis of COPD. Its literature search largely neglected citations on RCTs and general reference guideline on clinical trials protocols. Although the article indicated a plan to utilise ethical principles and guiding documents, it failed to cite them. The authors thus failed to demonstrate systematic scientific approach in designing the presented protocol. This removes the power of scientific rigour from the article.

**Stability:**

Published in the journal Trials, the article is adjured stable considering that the Journal, though of open access, is a peer-reviewed journal specially dedicated to clinical trial research that encompasses all aspects of the performance and findings of randomized controlled trials, included in PubMed and enjoys a global readership audience

**RECENT ADVANCES RELATED TO THE TOPIC**

Although public health related research is ubiquitous, a large gap exists between the volume and its transformation into clinical application and practice (Brownson et al. 2006). In the era of evidence-based medicine and the advances of clinical research targeted at the improvement of clinical practice in the care of patients, systematic application of translational research remains a burning issue hence a steady influx of new translational studies based on RCT.

In the ‘omic’ and human genome era, the concept of personalised medicine, rooted in the translation of individual genetic or molecular mechanism, has shifted from principle to practice (Waldman and Terzic, 2009; Terzic and Waldman, 2010)

CAM is another emerging health practice that has enjoyed growing attention in recent time. (Frenkel and Borkan, 2003). This growing attention emanates from a global demand for quality care and a greater interest by patients in personal health issues as evidenced in Australia, UK and USA (Shergis et al. 2013). The clinical research community have had to deal with obtaining the needed evidence for use of CAM, (Ernst, et al. 2004; Verhoef, et al. 2006). This evidence is useful for the translation and integration of CAM into modern clinical practice. Researchers have coined a specialty field called,
‘Translational Chinese Medicine’ and it is a current developing arm of clinical research, (Sun, et al. 2011). According to Ware et al. (2006), MEDLINE indexed articles in the past two decade indicate an increasing number of RCTs being undertaken by researchers to determine the efficacy and safety of CAM interventions.

The technical difference between Translational Chinese medicine and translational medicine according to Sun, et al., (2011), is that while translational medicine takes data from laboratory to bedside, translational Chinese medicine on the other hand takes data from bedside to laboratory and back while seeking clinical evidence. To do this, CAM researchers have strived to achieve scientific rigour through the design of study protocols that meet global gold standards in Clinical research. The Goal of this effort has been to integrate CAM therapies of proven safety and efficacy into healthcare and clinical practice.

CONCLUSION

This review was aimed at assessing the scientific and literary merit of the article as a translational research literature. The objective was to determine the degree of exploitation of existing knowledge in substantiating the principles, ethics and theories of developing a clinical research protocol to achieve its goal of measuring the efficacy and safety of an intervention.

In the cause of the review, it was observed that the article in its elaborate literature review provided a bibliography that was skewed in favour of the disease (COPD) in terms of its aetiology, prognosis and the use of ginseng as probable treatment. The subject of the article ‘study protocol for a randomised controlled trial’ was not given adequate attention. As a result of this, even though the authors were quite rigorous and eloquent in presenting the details of the protocol, they failed to highlight the guiding principles and theories to the uninformed reader. This and the fact that the work had errors in objective accuracy marred the scholarly quality of the article. However, the article presented a very clear methodological sequence of the protocol which could be exploited in RCT to test medical interventions.

This review thus concludes that the article provides information on the subject of RCT’s protocol development of complementary and alternative medicine. However, readers require seeking other necessary literature to fully appreciate the protocol.

REFERENCES


The objectives of this e-conference is to

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