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GRADUATION THESIS

Evidence-based recommendations of hemato-oncological guidelines: quality assessment and the role of industry-sponsored trials.

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Contents

ABSTRACT

Guidelines in clinical practice play a fundamental role in applying evidence-based medicine or professional guidance to clinical practice. An increasing financial conflict of interest in clinical trials in general medicine has been illustrated in recent literature. Pharmaceutical-funded clinical drug trials yield positive outcomes for company products more frequently than independent trials do. In this line, we aimed to identify whether there is a role of conflict of interest (COIs) in the hemato-oncology field.

Thus, we searched hemato-oncological guidelines (April 1st, 2007 and March 31st, 2017) from the selected transnational societies by the experts in the field of hemato-oncology. Clinical practice guidelines (CPGs) and consensus statements complying with the inclusion and exclusion criteria were included in the study and analysed the proportion of reported clinical trials funded by industry and non-industry for each guideline. Quality assessments were performed with the Appraisal of Guidelines for Research and Evaluation II (AGREE-II) tool.

We identified 110 guidelines, of which 57 were excluded; 53 guidelines included were developed by 7 transnational societies. Overall, we identified 927 treatment recommendations made by 507 trial citations, of which 255 (50.3%) were industry and 252 (49.7%) non-industry sponsored. The AGREE-II overall assessment score was less for specialised oncology developers (33.5%) than general guideline developers (52.8%). Of those six AGREE-II domains, the applicability domain scored (19.8%) less for the oncology specialised concerning general guideline developers (41.0%).

Concluding, we identified that the guidelines produced by ESMO, ELN and NCCN societies are driven to make recommendations by a greater proportion of industry-sponsored trials. The very low-quality score is reported in the guidelines established by the ELN, ESMO and NCCN society. Whereas AHS and BSH, medium-quality scores are registered. While the guidelines developed by CCO and NICE societies, higher quality scores are registered.

RIASSUNTO

Le linee guida nella pratica clinica svolgono un ruolo fondamentale nell'applicazione della medicina basata sull'evidenza o della guida professionale alla pratica clinica. Nella letteratura recente è stato illustrato un crescente conflitto di interessi finanziari negli studi clinici in medicina generale. Gli studi clinici sui farmaci finanziati da farmaci producono risultati positivi per i prodotti aziendali più frequentemente di quanto non facciano studi indipendenti. In questa linea, abbiamo mirato a identificare se esiste un ruolo del conflitto di interessi (COI) nel campo dell'emato-oncologia.

Pertanto, abbiamo cercato le linee guida emato-oncologiche (1 aprile 2007 e 31 marzo 2017) dalle società transnazionali selezionate dagli esperti nel campo dell'emato-oncologia. Le linee guida di pratica clinica (CPG) e le dichiarazioni di consenso conformi ai criteri di inclusione ed esclusione sono state incluse nello studio e hanno analizzato la proporzione di studi clinici segnalati finanziati dall'industria e non dall'industria per ciascuna linea guida. Le valutazioni della qualità sono state eseguite con lo strumento Appraisal of Guidelines for Research and Evaluation II (AGREE-II). Sono state identificate 110 linee guida, di cui 57 escluse; 53 linee guida incluse sono state sviluppate da 7 società transnazionali. Nel complesso, abbiamo identificato 927 raccomandazioni di trattamento formulate da 507 citazioni di studi, di cui 255 (50,3%) erano sponsorizzate dall'industria e 252 (49,7%) non dall'industria. Il punteggio complessivo della valutazione AGREE-II era inferiore per gli sviluppatori di oncologia specializzati (33,5%) rispetto agli sviluppatori di linee guida generali (52,8%). Di questi sei domini AGREE-II, il dominio di applicabilità ha ottenuto un punteggio inferiore (19,8%) per gli specialisti in oncologia riguardanti gli sviluppatori di linee guida generali (41,0%).

Concludendo, abbiamo identificato che le linee guida prodotte dalle società ESMO, ELN e NCCN sono spinte a formulare raccomandazioni da una percentuale maggiore di studi sponsorizzati dall'industria. Il punteggio di qualità molto basso è riportato nelle linee guida stabilite dalla società ELN, ESMO e NCCN. Mentre AHS e BSH, vengono registrati punteggi di qualità media. Nonostante le linee guida sviluppate dalle società CCO e NICE, vengono registrati punteggi di qualità più elevati.

1.) INTRODUCTION

1.1 Clinical practice guidelines (CPGs), Consensus statements

Clinicians widely use CPGs to inform patient care decisions. They are prepared by vigour's systematic review of evidence leading to recommendations intended for optimizing patient care. The Institute of Medicine (IOM) states, CPGs to be trustworthy and reliable, they should be transparent to minimize bias, conflicts of interest (COIs), and distortion.[1] whereas A 'consensus statement' is a public statement on a specific area of medical science, which is widely recognized as evidence-based, state-of-the-art knowledge by a representative community of experts in that discipline.

1.2 Conflicts of interest (COIs)

COI is defined as situations where the professional judgment concerning a primary interest (such as health and wellbeing of a patient or the validity of research), might be inappropriately influenced by a secondary interest (financial or non-financial).[2] Conflicts of interest and their possible negative consequences have been discussed concerning health care, medical research, physician's training and continuing education, and the creation of medical guidelines.[3] During the development process of CPGs, COI play an important role in the source of bias. Bias will result in an overestimation of benefit and an underestimation of harm[4], so that the biased CPGs may have dis-advantages to healthcare and patient outcomes. There are egress findings on COI, specific to industry relationships, clinical research.[5,6,7,8,9,10,11,12] Physicians' social and intellectual interests may also come into conflict.

Intellectual COI is defined as academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment for a specific recommendation.[13] Intellectual interests include the career developments in medical science, benefits from publication and getting research funding. These interests may be appropriate in themselves but may rise conflict with the interests of research subjects and patients.[14] Empirical data shows that the author's financial relationships or sponsor are associated with study outcomes[5-7,12] or decisions[11] favourable the industry.

Clinical trials financed by pharmaceutical companies are more likely to yield favourable results for the sponsor than trials performed Independently.[15,16] The recommendations presented in CPG were often not based on good evidence from clinical trials, but rather on expert opinion or standards of care.[17] Especially when adequate trial data are unavailable, the non-public opinions of the expert committee members can influence the recommendations that appear within the guideline. Identical data can be interpreted in a reverse way by different experts with or without conflicts of interest[18]. A study demonstrated that data that had been manipulated by the MAH (market authorization holder) of gabapentin served as a basis for recommendations to prescribe gabapentin in guidelines that were published by the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesell schaften).[19]

1.3 Clinical practice guideline development process

Every day, a physician must consider relevant management options concerning benefits and risks, burden and sometimes cost, evaluate patients' preferences and values to decide in the patient's best interests. In the last two decades, there was an increase in clinical practice guidelines developed to provide clinicians with information about the best treatment ways, with an explicit intent to influence physicians' behaviour. The process of guideline development should follow specific rules to avoid disagreement, misunderstanding, misleading recommendations, and confusion[20]. At the beginning of the development process, the topic will usually need to be defined. Through dialogue among clinicians, patients, and the potential users or evaluators of the guideline, the topic will be refined. If the topic that is not specific, the clinical condition or question may be too broad in scope[21].

The first step in guideline development involves knowing the target audience, the purpose and scope of the guidelines[22]. After this first step, the process must define a guideline panel that are the people who will be involved in the guideline development

process[23]. All guideline panel members must agree on the development process, define an explicit mechanism to obtain consensus and resolving the inevitable differences of opinion because they must work as a team[23]. In order to develop a successful guideline, it may be necessary to convene more than one group. Ideally, the group should have at least six but no more than 12-15 members[21]. The group that develop guidelines included: technical expertise, managers and health professionals, methodologist (statistics and health economist)[24]. The guideline panel begins its work by deciding on the priority accorded to specific clinical questions[25] regarding the population of interest, alternative approaches, and interest outcomes. One method of defining the clinical question of interest and identifying the processes for which evidence needs to be collected and assessed is constructing models or causal pathways[26]. A causal pathway is a diagram that shows the connection between interventions of interest and the intermediate, and health outcomes that the interventions are thought to influence[21]. All available evidence resulting from the answering of the clinical questions must be summarized[22]. This is done by conducting a systematic review for each clinical question asked. The purpose of a systemic review is to collect all available evidence to assess its potential applicability to the clinical questions. The first step is to see if suitable, recent systematic reviews have already been published during the evidence collection. The Cochrane Library will also identify relevant Cochrane review groups, which should also be contacted to see if a review in progress[21]. If fewer resources are available, one may search for and rely on existing systematic reviews if these are not available, on original studies. The users of the guidelines must understand the limitations of the recommendations[27]. Available evidence should be summarized in a clear tabular format showing the qualitative and quantitative effects of different management options. This summary of evidence is important to reflect their susceptibility to bias.[21] It is common to grade each recommendation in the guidelines. The grading defines the quality of evidence as the degree of confidence that an estimate of a given intervention's effect is adequate to support a recommendation. In this system of grading, randomized controlled trials typically provide high-quality evidence. The quality can be decreased to “moderate,” “low” or even “very low,” based on the factors

such as limitations in study design or execution, indirect nature of evidence, or inconsistency/ imprecision of the results.[20]

After assessing each critical outcome's quality of evidence separately, the guideline panel must determine the overall quality of evidence across all outcomes supporting a recommendation. Fundamental for guideline development is evaluating the balance between desirable (health benefits, less burden, lower cost) and undesirable effects (harm, burden, costs) of considered strategies. Then the evaluation, there is the formulation of recommendations that provide information about the population to which the recommended strategy and its alternative apply. This is important to give clear strategy's strengths to the users. If a guideline panel is confident, they formulate a strong recommendation ("we recommend…"). If the panel believes one option is still preferred to the other but is not confident, the resulting recommendation is weak ("we suggest…").[20]

Guidelines should submit to an external review to ensure content validity, clarity, and applicability. External reviewers are people with expertise in clinical content. They verify the completeness of the literature review and to ensure clinical sensibility.[21] Guidelines development strategy according to different societies described in **Table 1**.

Table 1: *Guideline development strategy of different guideline developers and their source of publication.*

Society	Website	Guideline development strategy	Source of guideline publication
AHS	www.albertahealthservices.ca	1. Identified guideline topic 2. Define research questions 3. Literature review 4. Review draft document 5. Submit final guideline to TLL 6. Publication 7. Maintenance *(Alberrtahealthservice.ca, (2017)*	Alberta Health Services (AHS) website.
BSH	www.b-s-h.org.uk	1. Topic identification 2. Search strategy and literature review 3. Grading evidence 4. Audit tool 5. Publication 6. Maintenance *(B-s-h.org, 2018)*	British Journal of Haematology (BSH) website and British journal of haematology
CCO	www.cancercare ontario.ca	1. Project planning 2. Document development: - identification and review of existing guidelines -systemic review evidence -recommendations development	Cancer Care Ontario (CCO) website

Society	Website	Guideline development strategy	Source of guideline publication
		3. Internal review 4. External review 5. Document completed 6. Journal publication 7. Maintenance *(Cancercareontario.ca, 2018)*	
ESMO	www.esmo.org	1. Guidelines development: - selection of relevant literature -summary recommendations - level of evidence and grades of recommendations have been applied. 2. Review 3. Publication *(Esmo.org 2019).*	European Society of Medical Oncology (ESMO) website and Journal: Annals of oncology
NCCN	www.nccn.org	1. Review data 2. Assign panel members 3. Assign level for each recommendation 4. Create an NCCN framework 5. Review and approval by the NCCN framework committee 6. Post preliminary version 7. Review international feedback 8. Post final version *(Nccn.org, 2019)*	National Comprehensive Cancer Network (NCCN) website and Journal of the National Comprehensive Cancer Network.

Society	Website	Guideline development strategy	Source of guideline publication
NICE	www.nice.org.uk	1. Topic chosen 2. Scope produced 3. Guideline development: - literature search -evidence reviews 4. Draft guideline sent for consultation 5. Comments considered; guidelines revised 6. Signed and publication 7. Maintenance *(Nice.org.uk, 2019)*	National Institute of Health and Care Excellence (NICE) website

1.4 Clinical trials

The International Conference of Medical Journal Editors defines clinical trials as "any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause and effect relationship between a medical intervention and a health outcome"[28]. These investigational trials determine whether experimental therapy, a new treatment, or new devices are safe and effective under controlled environments. For any new drug to enter a clinical trial, it must pass preclinical studies[29]. Some trials involve healthy members. Others involve patients who may be offered the option of taking part in a trial during their care and treatment. Clinical trials have a fundamental role in answering specific questions about health and illness[30]**.** The U.S. National Institutes of Health indicates seven ethical requirements that must be met before a clinical trial can begin: social value, scientific validity, fair and objective selection of subjects, informed consent, a favourable ratio

of risks to benefits, approval and oversight by an independent review board and respect for human subjects.

Clinical trials cover a wide range of different types of research. Some trials are used to test new medicines or vaccines but can also be used to look at new combinations of existing medicines. Other trials can also test whether administering a treatment differently will make it more effective or reduce any side effects. Some trials are designed to do out ways to stop a selected disease in those who have not had the disease or to stop a disease from returning. In these types of experimental studies, are include vaccines, drugs, or dietary supplements. Other experimental trials can be used to test 'interventions' aimed at modifying a person's behaviour or lifestyle[30]. People of all ages can participate in clinical trials. They need to respect eligibility criteria. In the inclusion of children, the parents or guardians must decide if they want their child to participate. If the parents give permission, older children are usually asked whether they wish to take part. This process is called "assent".

In most cases, a child can refuse, even if the parents are willing to permit it. The process of considering a clinical trial is much the same for the parents of a child as it is for an adult[31]. When in clinical trials is present a diverse population participates, there is an increase in the potential to know more about different subgroups. Males and females, young and old, people of various racial and ethnic backgrounds, and patients with different diseases condition might respond differently to a medical product[32].

Before being considered reasonably safe and effective, every new treatment must be tested in four phases of clinical trials[31]. The first three are designed to establish safety and efficacy, while Phase IV, that is, post-marketing trials gives additional information regarding new indications, risks, and optimal doses and schedules.

1.4.1 Phases of clinical trials

Phase-I

In this phase, the investigator will test a replacement biomedical intervention in a small group of individuals (20-80) to gauge safety for the primary time.

Phase-II

Research of biomedical or behavioural intervention in a very large number of individuals (several hundred) to see its effectiveness and further assess its safety.

Phase-III

The physicians will investigate the efficacy of the biomedical or behavioural intervention in large groups of human subjects by comparing the intervention to other standard or experimental interventions similarly on monitor adverse effects and collecting information that can allow the intervention to be used safely.

Phase-IV

They are conducted after the intervention has been marketed. These studies are designed to look at the effectiveness of the approved intervention within the general population and to collect information about any adverse effects associated with widespread use.[33]

In order to demonstrate efficacy, the Food and Drug Administration requires performing "adequate and well-controlled investigations," generally interpreted to mean two replicate clinical trials that are usually, but not always, randomized, double-blind, and placebo-controlled.

The most important barrier to completing clinical trials is that not enough people take part in them: <5% of adults (less than 1 in 20) with cancer will participate in a clinical trial. Clinical trials are much more commonly used to treat children with cancer. 60% of children <15 years participate in clinical trials. This is one reason why childhood cancer's survival rates have dramatically increased in the last few decades.[31]

1.5 Clinical trial registry

In recent years, the important role of publicly accessible information on clinical research has become widely accepted.[34] Knowledge of the clinical trials' currently active status provides greater access to enrollment options for patients and further supports ongoing medical advancements to treat or help prevent the disease. Public access to the evidence resulted in clinical trials improves health care and medical decision.

The necessity of clinical trials registration has long been demonstrated at the global level. The first clinical trials registry in history was clinicaltrial.gov. It was created because of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA required the U.S. Department of Health and Human Services (HHS), through National Institute of Health (NIH), to provide a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions *(https://www.clinicaltrials.gov)*.

In November 2004 at the Ministerial Summit on Health Research, all participants demanded interventions by all major stakeholders, facilitated by the World Health Organization (WHO) secretariat, to establish a platform for linking of all international clinical trials registries to ensure a single point of access and unambiguous identification of trials.

In 2006, it was founded the International Clinical Trials Registry Platform (ICTRP) available at http://apps.who.int/trialsearch/. This platform has been included 17 clinical trial registries of different nationality **[Table 2]**. It points is to make: "a willful stage to connect clinical preliminaries registers to guarantee a solitary purpose of access and the unambiguous recognizable proof of preliminaries with the end goal of upgrading admittance to data by patients, families, quiet gatherings and others.[35]

Any registry that includes clinical trials into its database prospectively and meets the WHO Registry Criteria, or working with the ICTRP towards meeting these criteria,

can be part of the WHO Registry Network. Primary Registries in the WHO Registry Network are those that meet all WHO Registry Criteria.[36]

Primary Registries must also meet the requirements criteria of the International Committee of Medical Journal Editors (ICMJE) in which the registration of clinical trials is a prerequisite for consideration of clinical trial data publication.[37]

Partner Registries in the WHO Registry Network must meet most, but not all, of the criteria. Specifically, they are not required to have a national mandate, and they can be limited in the purpose. The registries in the WHO Registry Network are separated in remit and functionality. Minimum standards need to be determined and implemented to harmonise how data are collected and validated by these registries, thus ensuring a baseline level of data quality. Participating registries, in this way, will improve the usability of the ICTRP Search Portal and facilitate the searching of information about clinical trials.[36]

To be recognized as a Primary Registry in the WHO Registry Network, they must unambiguous identification, technical capacity, and administration and governance. Registries are accountable for ensuring they need internal control processes and procedures to ensure compliance with all the minimum international standards defined during this document.[36] Despite these international regulations, there have been growing concerns and fears that due to vested interests, negative trial results are often not brought to the notice of the general public and physicians.

The significance of the presence of clinical preliminaries vaults is exhibited in India, in which Vioxx debate[38] reports the presence of deceptive clinical preliminaries led without legitimate leeway from important specialists or appropriate harmfulness examines. These events have brought to the urgent need for registration of all clinical trials. With this scenario, the Clinical Trials Registry – India (CTRI) was established at the National Institute of Medical Statistics, Indian Council of Medical Research (ICMR), New Delhi in 2007. The CTRI is an online and public, searchable platform wherein clinical trials conducted in India may be registered while declaring certain

information regarding the trial. The registry aims to provide a public record system by registering all clinical trials concerning drugs, devices, vaccines, and herbal drugs. The vision is to extend awareness and accountability of all the clinical trials participants and public access to push training, assistance, and advocacy for clinical trials by creating database and modules of study for various aspects of clinical trials and their registration.[37]

Clinical trials registries and clinical results databases differ in their purposes. Clinical trials registries provide information on ongoing and completed clinical trials to the public. Additional patients may or may not be enrolling in ongoing trials. Clinical trials are included in the registry at or near the trial beginning and were initially used to study interventions for rare and/or life-threatening diseases. The purpose was to provide access to experimental therapies through the dissemination of limited information about these studies.

Recently, the intention of registries has changed to incorporate all therapeutic areas and kinds of interventions. Results databases were established to obtain transparency in the presentation of clinical trials, which concerns that publication of clinical trials results was selectively biased toward "positive" trials in which the tested hypothesis was proven. Databases were designed to demonstrate and provide full veracity of positive and negative trial results. The presumed result of such disclosure is to provide a complete view of the data available for a particular drug or intervention and allow the use of existing data to guide subsequent clinical trials. Database address concerns that investigators or sponsors are also less inclined to publish negative trial results which journal editors may also be less inclined to accept manuscripts describing negative studies for publication[28].

Table 2 *Primary registries in International clinical trials registry platform (ICTRP).*

N	Registry name	Country
1	Australian New Zealand Clinical Trials Registry.	Australian, New Zealand.
2	Chinese Clinical Trial Registry.	China.
3	ClinicalTrials.gov.	USA.
4	EU Clinical Trials Register (EU-CTR).	European Union.
5	ISRCTN.	UK.
6	The Netherlands National Trial Register.	Netherlands.
7	Brazilian Clinical Trials Registry (ReBec).	Brazil.
8	Clinical Trials Registry India.	India.
9	Clinical Research Information Service	The Republic of Korea.
10	Cuban Public Registry of Clinical Trials.	Cuba.
11	German Clinical Trials Register.	Germany
12	Iranian Registry of Clinical Trials.	Iran.
13	Japan Primary Registries Network.	Japan.
14	Pan African Clinical Trial Registry.	Africa.
15	Sri Lanka Clinical Trials Registry.	Sri Lanka.
16	Thai Clinical Trials Registry (TCTR).	Thailand.
17	Peruvian Clinical Trials Registry (REPEC).	Peru.

1.6 Appraisal of Guidelines for Research and Evaluation II (AGREE-II)

The potential benefits of guidelines are related to the quality of the guidelines themselves. High-quality CPGs are fundamental for improving healthcare management, as they are special tools that translate scientific research findings, provide explicit recommendations, and support evidence-based decision making.[39,40] Their quality can be extremely variable.[41,42] Organization characteristics were shown to be responsible for a large part of the variation in quality score.[43] Clinical practice

guidelines result from having higher methodological quality in comparison to consensus statements.[44] Existing literature reported that the quality of clinical practice guidelines is modest in general medicine, but oncology guidelines seem to be better for certain domains.[42] Various studies have demonstrated that CPGs that suffer from low to moderate quality call into question the reliability of such measures among healthcare professionals and managers.[45,46,47,48,49,50,51,52,53] Many tools have been developed across the globe for evaluating the quality of CPG.[54,55]

The Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument (AGREE collaboration, 2003) was developed to avoid variability in guideline quality. This instrument is a tool that assesses the methodological rigour and transparency in which a guideline is developed. In 2003, the original AGREE Instrument was published by a group of international guideline developers and researchers, the AGREE Collaboration[56].

1.6.1 AGREE-II Instrument

The AGREE Next Steps Consortium (May 2009), updated in September 2013,[57] was used in this project for quality evaluation of CPGs. It contains 6 domains consisting of 23 key items **[Table 3]**.

1.6.1.1 Scope and Purpose: The ultimate purpose of the guidance, the relevant health problems and the target demographic are discussed (items 1-3).

1.6.1.2 Stakeholder Involvement: It focuses on the degree to which the relevant stakeholders established the guidance and reflected its intended users' views. (items 4-6).

1.6.1.3 Rigour of Development: It relates to the process used to collect and synthesize the evidence, the techniques for formulating and updating the recommendations. (items 7-14).

1.6.1.4 Clarity of Presentation: The language, structure and format of the Guideline are discussed (items 15-17).

1.6.1.5 Applicability: The potential challenges and facilitators to adoption, methods for enhancing uptake and the resource consequences of applying the guideline are concerned (items 18-21).

1.6.1.6 Editorial Independence: It is concerned with making recommendations is not unduly biased against competing interests. (items 22-23).

1.6.1.7 Overall assessment: This includes the overall quality rating of the guideline and whether it will be advised to use the guideline in practice.

Table 3: *AGREE-II Quality evaluation tool: Six domains with 23 key items.*

Item	Content	Domain
1	The overall objective(s) of the guideline is (are) specifically described.	Scope and Purpose
2	The health question(s) covered by the guideline is (are) specifically described.	
3	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	
4	The guideline development group includes individuals from all relevant professional groups.	Stakeholder Involvement
5	The views and preferences of the target population (patients, public, etc.) have been sought.	
6	The target users of the guideline are clearly defined.	
7	Systematic methods were used to search for evidence.	Rigour of Development
8	The criteria for selecting the evidence are clearly described.	
9	The strengths and limitations of the body of evidence are clearly described.	
10	The methods for formulating the recommendations are clearly described.	
11	The health benefits, side effects, and risks have been considered in formulating the recommendations.	
12	There is an explicit link between the recommendations and the supporting evidence.	
13	The guideline has been externally reviewed by experts prior to its publication.	
14	A procedure for updating the guideline is provided.	
15	The recommendations are specific and unambiguous.	Clarity of Presentation
16	The different options for management of the condition or health issue are clearly presented.	
17	Key recommendations are easily identifiable.	
18	The guideline describes facilitators and barriers to its application.	Applicability
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	
20	The potential resource implications of applying the recommendations have been considered.	
21	The guideline presents monitoring and/or auditing criteria.	
22	The views of the funding body have not influenced the content of the guideline.	Editorial Independence
23	Competing interests of guideline development group members have been recorded and addressed.	

2.) AIM OF THE THESIS

AIMS OF THE THESIS

The quality assessment of haemato-oncological CPGs developed by the transnational societies using AGREE-II tool and quantify the proportion of industry-sponsored *vs* non-industry sponsored trial citations per guideline.

3.) MATERIALS AND METHODS

3.1 Search strategy

Selected databases/websites were searched for haemato-oncological guidelines concerning leukaemia, lymphoma, multiple myeloma. Different national, International societies were searched, i.e. Alberta health services (AHS)[58], American Society of Haematology (ASH)[59], American Society of Clinical Oncology (ASCO)[60], British Society for Haematology (BSH)[61], Cancer Care Ontario (CCO)[62], Cancer Council Australia (CCA)[63], European Leukaemia Net (ELN), European Society of Medical Oncology (ESMO)[64], National Comprehensive Cancer Network (NCCN)[65], National Institute for Health and Care Excellence (NICE)[66], Scottish Intercollegiate Guidelines Network (SIGN)[67]. In addition to searching these societies' websites, PubMed was also searched for guidelines released by these societies. PubMed search terms were: Guideline, practice guideline, consensus conference development. Acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, diffuse large B-cell lymphoma, essential thrombocythemia, follicular lymphoma, hairy cell leukaemia, Hodgkin's lymphoma, mantle cell lymphoma, mature B-cell neoplasms, mature T- and NK-cell neoplasm, myelodysplastic syndromes, myeloproliferative neoplasms, polycythaemia vera, primary myelofibrosis, Waldenstrom macroglobulinemia. Guidelines published as on March 31st, 2017 were searched.

3.2 Inclusion and exclusion criteria of guidelines

Guidelines and consensus statements were included in the analysis if: i) had been developed by transnational societies for haematological malignancies (leukaemia, lymphoma, multiple myeloma); ii) were published in the English language; iii) at least one trial identifier was used in the publication to make treatment recommendations. As a rule, the most recent version of the guideline was considered to expect for ELN society for each society. Guidelines without specific recommendations, guidelines with an update in progress, technology assessment guidelines, guidelines that had been archived, guidelines used for education and information purpose, health system guidelines, and evidence summary documents were excluded from the study. We included only the publication cited with trial identifiers for analysis (*industry vs non-industry*).

3.3 Quality assessment of guidelines

Quality of the guidelines was assessed using Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool, an instrument internationally and validated used to assess the quality of practice guidelines with a focus on the methodological development and transparency.[68,69,70] Initially, two appraisers were trained in the AGREE-II tool using the online tutorial available at http://www.agreetrust.org/. Agree-II contains 6 domains (Scope and Purpose, Stakeholder Involvement, Rigour of Development, Clarity of Presentation, Applicability and Editorial Independence), consisting of 23 key items and an additional two global rating items for an "Overall Assessment" of the practice guideline. Each item was rated on a scale from 1-7 by two appraisers, and the total score for each domain was calculated as described in AGREE II with the formula: [(score obtained–minimum score possible)/ (maximum score possible–minimum score possible)] x 100. Therefore, the minimum value for the standardized domain score is 0%, and the maximum is 100%. According to AGREE-II, the six domain scores were considered separately, and a final overall assessment score was given agreed by the two appraisers. The mean item and standardized domain scores of the oncology specialised guideline developers were compared with those of the general guideline developers. All discrepancies were discussed between the appraisers and a specialist in the AGREE-II instrument.

3.4 Classification of hemato-oncological guidelines

Included guidelines were classified according to WHO classification.[71,72] Leukemia includes as Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Myeloproliferative Neoplasm (MPN), Myelodysplastic Syndrome (MDS), Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML). Lymphoma includes B-cell lymphoma (BCL), Diffuse Large B-cell Lymphoma (DLBCL), Extra nodal Diffuse Large B-cell Lymphoma (Extra nodal DLBCL), Follicular Lymphoma (FL), Hairy Cell Lymphoma (HCL), Hodgkin's Lymphoma (HL), Mantle Cell Lymphoma (MCL), Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), Non-Hodgkin's Lymphoma (Non-HL), Primary Cutaneous lymphomas (PCL), Peripheral T-cell Lymphomas (PTCL), T-cell lymphomas (TCL) and Waldenstrom's macroglobulinemia (WM).

3.5 Data extraction and analysis

Data were extracted from the include hemato-oncological guidelines, the guideline title, recommendation description, year of publication, level of evidence, and grade of recommendation. Articles cited to make recommendations were retrieved. Trial identifiers were extracted from the published papers. Trial identifiers were used to search the trial registries to extract information regarding funder type (*industry or non-industry*), sponsors, and collaborators. Funder type was classified according to the registry. The analysis focused on the proportion of industry-sponsored *vs* non-industry sponsored registered studies with trial identifiers cited in the publication and used to make recommendations. Trials without trial identifier were not considered. The duplicates citations were removed for each disease type to obtain the true frequency proportion between industry vs non-industry trials. In this way, the real frequency of registered clinical trials was obtained.

4.) RESULTS

4.1 Haematological guidelines identified by the search strategy

Hundred and ten records of haematological guidelines were identified, of which 57 were excluded based on the criteria adopted in this study **[Figure 1]**. In total, 53 guidelines on leukaemia, lymphoma and multiple myeloma developed by 7 scientific societies were selected **[Table 4]**. The ESMO developed Seventeen guidelines, 10 by the NCCN, BSH-9, NICE-2, AHS-2, CCO-4, and ELN-4 guidelines. All included guidelines were further scored for quality assessment by AGREE-II.

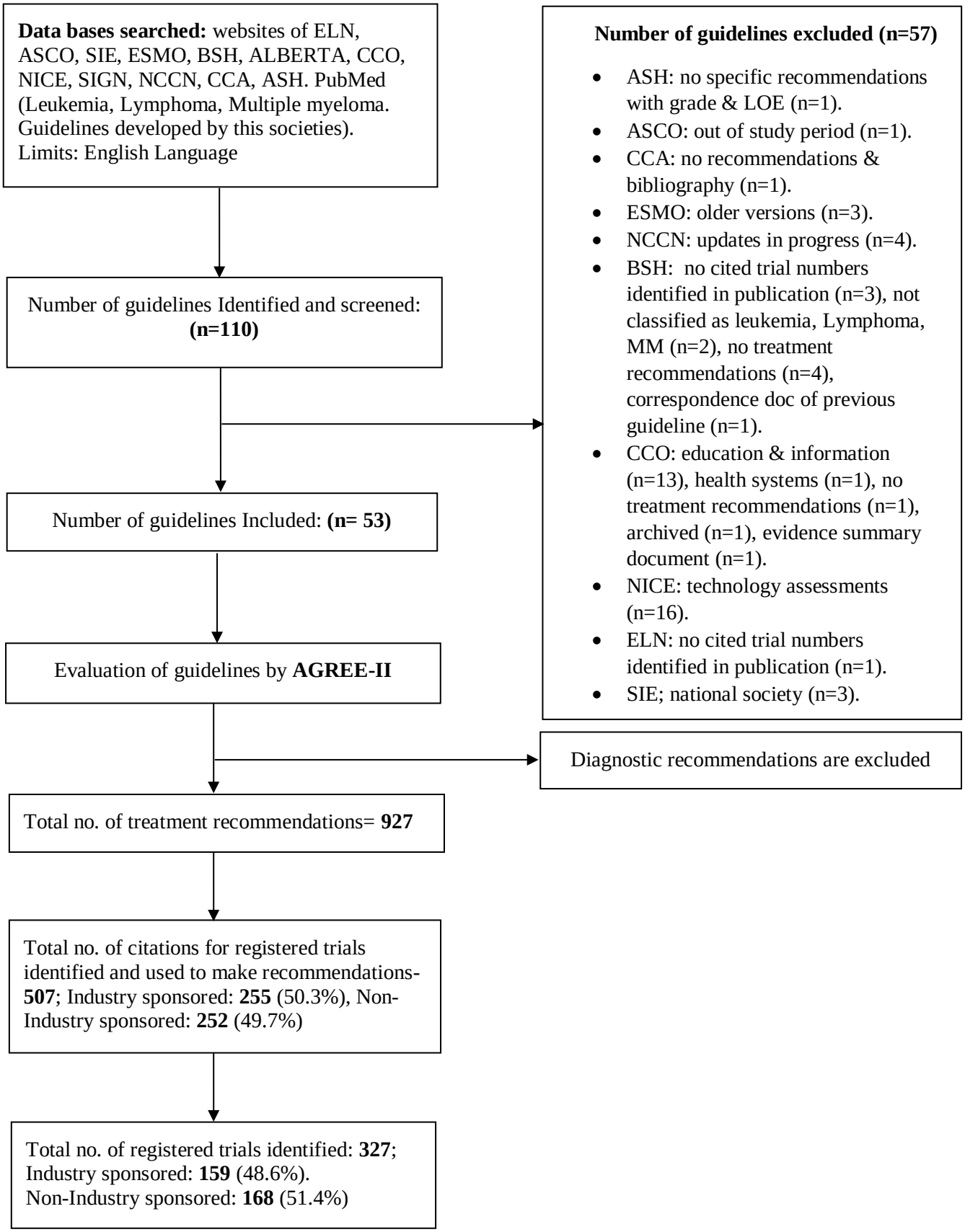
Out of the 53 guidelines, 927 treatment recommendations were identified. The total number of registered trial citations used to make treatment recommendations was 507, of which 255 (50.3%) referred to industry-sponsored studies and 252 (49.7%) to non-industry sponsored studies. Only clinical trials registered in a public database were considered, namely clinicaltrials.gov (www.clinicaltrials.gov), Chinese clinical trial registry (www.chictr.org.cn), Australian New Zealand's clinical trial registry (www.anzctr.org.au), EudraCT (www.clinicaltrialsregister.eu), Netherlands trial Register (www.trialregister.nl), ISRCTN (www.isrctn.com), UMIN-CTR Clinical Trial registry (www.umin.ac.jp/ctr). After removal of duplications, the total number of registered trials cited by the 927 recommendations was 327, of which 159 (48.6%) industry-sponsored and 168 (51.4%) non-Industry sponsored **[Figure 1]**

Table 4 *53 Included Haematological Malignancies guidelines (Leukemia, Lymphoma, Multiple myeloma) of various transnational societies.*

Society	Country	Title of Guideline	Year
European Society of Medical Oncology	Switzerland	CML-Diagnosis, treatment, follow-up [73]	2012
		AML-Diagnosis, treatment, follow-up [74]	2013
		Myelodysplastic syndromes [75]	2014
		CLL-Diagnosis, treatment, follow-up [76]	2015
		Hairy cell Leukaemia [77]	2015
		chronic myeloproliferative Neoplasms [78]	2015
		ALL-Diagnosis, treatment, follow-up [79]	2016
		waldenstroms macroglobulinemia [80]	2013
		Primary cutaneous Lymphomas [81]	2013
		Gastric marginal lymphoma of MALT-Type [82]	2013
		Newly Diagnosed and relapsed mantle cell Lymphoma [83]	2014
		Hodgkin's Lymphoma [84]	2014
		peripheral T-cell Lymphomas [85]	2015
		DLBCLS [86]	2015
		Newly Diagnosed and relapsed Follicular Lymphoma [87]	2016
		Extra nodal diffuse large B-cell lymphoma & primary mediastinal B-cell Lymphoma [88]	2016
		Multiple Myeloma [89]	2013
National comprehensive cancer network	United States	Acute Lymphoblastic Leukaemia [90]	2016
		Acute Myeloid Leukaemia [91]	2016
		Chronic Lymphocytic Leukaemia/ Small Lymphocytic Lymphoma[92]	2017
		Chronic Myelogenous Leukaemia (Evidence Blocks) [93]	2016
		Hodgkin Lymphoma [94]	2017
		Non-Hodgkin's Lymphoma-DLBCL (Evidence Blocks) [95]	2016
		Multiple Myeloma (Evidence Blocks) [96]	2016
		Myelodysplastic Syndromes (Evidence Blocks) [97]	2016
		Waldenstroms Macroglobulinemia/Lymphoplasmacytic Lymphoma[98]	2016
		Myeloproliferative Neoplasms[99]	2016
British Society of Haematology	United Kingdom	Diagnosis and Management of Adult Myelodysplastic syndromes [100]	2014
		Diagnosis and Management of Chronic Lymphocytic Leukaemia [101]	2012
		Diagnosis and Management of Myelofibrosis [102]	2012
		Management of primary resistant and relapsed classical Hodgkin's Lymphoma [103]	2014
		First-line Management of Classical Hodgkin's Lymphoma [104]	2014
		Management of Mantel cell Lymphoma [105]	2012
		Management of Nodular Lymphocyte Predominant Hodgkin Lymphoma [106]	2016
		Diagnosis and Management of Waldenstrom Macroglobulinemia [107]	2014
		Guidelines for the management of Diffuse large B-cell Lymphoma [108]	2016
Alberta Health Services	Canada	Management of Chronic Myeloid Leukaemia [109]	2015
		Acute Lymphoblastic Leukaemia [110]	2016
		Acute Myeloid Leukaemia [111]	2015
		Chronic Lymphocytic Leukaemia [112]	2015
		Lymphoma [113]	2016
		Myelodysplastic syndromes [114]	2009
		Multiple Myeloma [115]	2015

Cancer Care Ontario	Canada	Systemic Treatment of Acute Myeloid Leukaemia [116] Lenalidomide in Multiple Myeloma [117] Bortezomib in Multiple myeloma [118] Management of Early-stage Hodgkin Lymphoma [119]	2016 2012 2014 2015
National Institute of Health care and Excellence	United Kingdom	Non-Hodgkin's lymphoma: diagnosis and management [120] Myeloma: diagnosis and management [121]	2016 2016
European Leukaemia Net Foundation	Germany	CML: Management recommendations [122] CML: Management recommendations [123] CML: Management recommendations [124] Philadelphia-Negative Classical Myeloproliferative Neoplasms [125]	2009 2013 2015 2011

Figure 1 Flow Chart OF Guideline Selection



4.2 Individual guideline quality assessment with AGREE-II tool

Two appraisers evaluated the included guidelines developed by transnational societies using AGREE-II tool. The individual domain scores of each guideline were represented in **Table 5.** Very low-quality scores are recorded in guidelines developed by ESMO society. Their overall quality assessment is registered between 8%-33%. Low-quality scores were recorded for the guidelines developed by ELN, *i.e.*, between 17%-33%. AHS and BHS's guidelines were recorded with a medium quality; their overall quality assessment is between 33%-58%. The higher quality assessment score was recorded in guidelines released by CCO and NICE guidelines; they record an overall quality assessment score between 67%-83%.

4.3 Quality assessments of guidelines by disease-specific

We classified the guidelines by disease-specific and analysed the mean domain scores. If the domain is reported with greater than 60%, we recorded it as high quality, from 40-60% as medium quality, 40-30% low-quality domain and if less than 30% we considered it a very quality domain. The same phenomenon was applied to the overall assessment.

4.3.1 AML guidelines

The mean domain scores (%) of 4 AML guidelines developed transnational societies were analysed. Of those six domains, clarity of presentation (69.3%) and scope and purpose (63.8%), recorded a high-quality score. In contrast, editorial independence (55.3%) and rigour of development (52.8%) were reported medium quality scores. A low-quality score was registered for stakeholder involvement (37.5%), followed by very low-quality scores for the applicability domain, with 21.0% recorded. The overall mean assessment was 44% and was recorded as medium quality.

4.3.2 ALL guidelines

For three ALL guidelines, clarity of presentation (69.3%) domain registered with high-quality scores. In contrast, medium quality scores were reported for the scope and purpose (49.0%) and rigour of development (45.7%) domains. While low-quality scores were obtained for editorial independence (33.3%) and stakeholder involvement (31.3%) domains followed by very low-quality scores for applicability (21.7%) domain were recorded. Overall, the average consistency of ALL guidelines (n=3) reported poor at 33.3%.

4.3.3 MPN guidelines

For four MPN guidelines, we evaluated six domains, the scope and purpose (56.3%), clarity of presentation (55.5%), editorial independence (46.0%), and rigour of development (43.5%), domains registered with medium quality scores. Whereas stakeholder involvement (34.5%), domain reported low-quality percentages, followed by applicability (19.8%) domain with very quality scores were recorded. Overall, the average final evaluation was low, i.e., 31.3% for 4 MPN guidelines.

4.3.4 CML guidelines

For six CML guidelines, we analysed the quality score for six domains. Of those 6 domains, the clarity of presentation (61.0%) was reported with high-quality percentage. Whereas the editorial independence (52.3%) and scope and purpose (43.2%) medium quality scores were registered. While rigour of development (33.7%) domain recorded with low scores, followed by stakeholder involvement (25.5%) and applicability (23.7%) recorded very low-quality scores. In overall, the mean assessment (29.0%) was very low for CML guidelines.

4.3.5 MDS guidelines

We analysed four MDS guidelines the quality of six domains. The clarity of presentation (75.8%) with a high percentage of the quality score was recorded from those 6 domains, in comparison, medium quality scores were reported for the rigour of development (52.3%), editorial independence (51.0%), and scope and purpose (46.8%). While stakeholder involvement (33.3%) reported low-quality scores in the domain, the very low-quality score was reported in the applicability (24.5%) domain. A final overall assessment (37.8%) score was low for MDS guidelines.

4.3.6 CLL guidelines

For four CLL guidelines, we assessed the six domains. Of those 6 domains, the clarity of presentation (73.0%) a high percentage of quality scores were registered, compared to medium quality scores for the rigour of development (52.3%), and scope and purpose (47.3%). Whereas the stakeholder involvement (38.0%) and editorial independence (38.8%) recorded lower quality percentages. Whilst the applicability (24.0%) domain reported very low-quality score among the 6 domains. The final overall assessment (35.5%) was low for CLL guidelines.

4.3.7 Lymphoma guidelines

For 22 Lymphoma guidelines, the six quality domains were evaluated. Among the 6 domains, the clarity of presentation (67.1%) reported a higher score. While the editorial independence (51.3%), the rigour of development (50.0%), scope and purpose (49.5%) and stakeholder involvement (45.0%) domains obtained medium quality percentages. Whereas the applicability (19.7%) domain reported very low-quality score. In overall, the final overall evaluation was low for lymphoma guidelines, i.e. 34.6%.

4.3.8 Multiple myeloma guidelines

Six Multiple myeloma guidelines were analysed. Of those 6 domains; the clarity of presentation (69.0%), editorial independence (65.3%), scope and purpose (65.0%) and rigour of development (64.7%) domains recorded high-quality scores. Whereas medium quality scores were obtained for stakeholder involvement (52.3%) and applicability (40.7%) domains **[Table 6]**. The overall quality assessment (52.8%) was reported as a medium for the MM guidelines

Table 5: *Quality Assessment by AGREE-II Instrument: 6 Domain scores of 53 guidelines appraised by two evaluators.*

N	Society	Guideline title	Publication	Scope & Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
1	ESMO	CML-Diagnosis, treatment, follow-up	2012	36%	22%	40%	97%	27%	63%	25%
2	ESMO	AML-Diagnosis, treatment, follow-up	2013	47%	28%	38%	75%	13%	46%	17%
3	ESMO	Myelodysplastic syndromes	2014	50%	33%	43%	75%	17%	46%	17%
4	ESMO	CLL-Diagnosis, treatment, follow-up	2015	36%	39%	38%	53%	21%	46%	17%
5	ESMO	Hairy cell Leukemia	2015	53%	36%	40%	50%	21%	46%	17%
6	ESMO	chronic myeloproliferative Neoplasms	2015	64%	44%	52%	83%	29%	50%	33%
7	ESMO	ALL-Diagnosis, treatment, follow-up	2016	58%	39%	40%	72%	19%	46%	25%
8	ESMO	waldenstroms macroglobulinaemia	2013	33%	28%	27%	58%	23%	42%	17%
9	ESMO	Primary cutaneous Lymphomas	2013	25%	33%	30%	56%	8%	46%	17%
10	ESMO	Gastric marginal zone lymphoma of MALT type	2013	25%	31%	27%	58%	19%	46%	17%
11	ESMO	Newly Diagnosed and relapsed mantle cell Lymphoma	2014	28%	33%	28%	72%	10%	46%	17%
12	ESMO	Hodgkin’s Lymphoma	2014	36%	31%	34%	75%	10%	46%	17%

N	Society	Guideline title	Publication	Scope & Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
13	ESMO	peripheral T-cell Lymphomas	2015	31%	33%	27%	44%	8%	46%	8%
14	ESMO	DLBCLS	2015	36%	31%	36%	81%	10%	46%	17%
15	ESMO	Newly Diagnosed and relapsed Follicular Lymphoma	2016	28%	33%	31%	75%	10%	46%	17%
16	ESMO	Extra nodal large B-cell lymphoma& mediastinal B-cell Lymphoma	2016	61%	50%	35%	69%	13%	46%	17%
17	ESMO	Multiple Myeloma	2013	33%	33%	24%	36%	13%	46%	0%
18	NCCN	Acute Lymphoblastic Leukemia	2016	47%	36%	52%	47%	31%	33%	42%
19	NCCN	Acute Myeloid Leukemia	2016	44%	36%	56%	47%	19%	33%	42%
20	NCCN	Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma	2017	28%	44%	54%	53%	23%	33%	33%
21	NCCN	Chronic Myelogenous Leukemia (CML-NCCN Evidence Blocks)	2016	25%	19%	56%	50%	29%	63%	33%
22	NCCN	Hodgkin Lymphoma	2017	53%	44%	58%	61%	40%	50%	42%
23	NCCN	Non-Hodgkin's Lymphoma-DLBCL Evidence Blocks	2016	42%	44%	44%	56%	25%	42%	42%
24	NCCN	Multiple Myeloma (Evidence Blocks)	2016	33%	42%	57%	53%	35%	63%	42%

N	Society	Guideline title	Publication	Scope & Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
25	NCCN	Myelodysplastic Syndromes (Evidence Blocks)	2016	42%	39%	51%	50%	31%	54%	42%
26	NCCN	Waldenstroms Macroglobulinemia/Lymphoplasmacytic Lymphoma	2016	28%	36%	52%	42%	19%	42%	42%
27	NCCN	Myeloproliferative Neoplasms	2016	42%	22%	46%	44%	27%	46%	33%
28	BSH	Diagnosis and Management of Adult Myelodysplastic syndromes	2014	42%	47%	61%	81%	19%	54%	42%
29	BSH	Diagnosis and Management of Chronic Lymphocytic Leukemia	2012	53%	50%	64%	86%	25%	38%	42%
30	BSH	Diagnosis and Management of Myelofibrosis	2012	72%	50%	60%	78%	19%	46%	42%
31	BSH	Management of primary resistant and relapsed classical Hodgkin's Lymphoma	2014	92%	53%	70%	89%	19%	71%	58%
32	BSH	First line Management of Classical Hodgkin's Lymphoma	2014	56%	58%	72%	86%	21%	58%	50%
33	BSH	Management of Mantel cell Lymphoma	2012	58%	58%	71%	75%	2%	63%	42%
34	BSH	Management of Nodular Lymphocyte Predominant Hodgkin Lymphoma	2016	61%	69%	72%	75%	6%	42%	58%

N	Society	Guideline title	Publication	Scope & Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
35	BSH	Diagnosis and Management of Waldenstrom Macroglobulinemia	2014	44%	33%	54%	83%	19%	29%	33%
36	BSH	Guidelines for the management of Diffuse large B-cell Lymphoma	2016	81%	69%	72%	75%	4%	58%	58%
37	ALBERTA	Management of Chronic Myeloid Leukemia	2015	64%	22%	36%	94%	38%	38%	58%
38	ALBERTA	Acute Lymphoblastic Leukemia	2016	42%	19%	45%	89%	15%	21%	33%
39	ALBERTA	Acute Myeloid Leukemia	2015	72%	22%	34%	72%	23%	42%	50%
40	ALBERTA	Chronic Lymphocytic Leukemia	2015	72%	19%	53%	100%	27%	38%	50%
41	ALBERTA	Lymphoma	2016	72%	25%	45%	36%	52%	38%	42%
42	ALBERTA	Myelodysplastic syndromes	2009	53%	14%	54%	97%	31%	50%	50%
43	ALBERTA	Multiple Myeloma	2015	72%	39%	54%	72%	33%	33%	50%
44	CCO	Systemic Treatment of Acute Myeloid Leukemia	2016	92%	64%	83%	83%	29%	100%	67%
45	CCO	Lenalidomide in Multiple Myeloma	2012	86%	61%	88%	92%	42%	100%	83%
46	CCO	Bortezomib in Multiple Myeloma	2013	94%	58%	83%	92%	46%	75%	67%

N	Society	Guideline title	Publication	Scope & Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
47	CCO	Management of Early-stage Hodgkin Lymphoma	2015	69%	75%	91%	83%	19%	100%	67%
48	NICE	Non-Hodgkin's lymphoma: diagnosis and management	2016	78%	86%	83%	78%	75%	79%	67%
49	NICE	Myeloma: diagnosis and management	2016	72%	81%	82%	69%	75%	75%	75%
50	ELN	CML: Management recommendations	2009	50%	31%	35%	69%	21%	54%	33%
51	ELN	CML: Management recommendations	2013	53%	31%	27%	39%	27%	63%	25%
52	ELN	CML: Management recommendations	2015	31%	28%	8%	17%	0%	33%	0%
53	ELN	Philadelphia-Negative Classical Myeloproliferative Neoplasms	2011	47%	22%	16%	17%	4%	42%	17%

Table 6: *Guidelines by Disease-specific: Quality Assessments By AGREE-II.*

Disease	No. of guidelines	Mean Domain scores (%)						
		Scope & Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
AML	4	63.8%	37.5%	52.8%	69.3%	21.0%	55.3%	44.0%
ALL	3	49.0%	31.3%	45.7%	69.3%	21.7%	33.3%	33.3%
MPN	4	56.3%	34.5%	43.5%	55.5%	19.8%	46.0%	31.3%
CML	6	43.2%	25.5%	33.7%	61.0%	23.7%	52.3%	29.0%
MDS	4	46.8%	33.3%	52.3%	75.8%	24.5%	51.0%	37.8%
CLL	4	47.3%	38.0%	52.3%	73.0%	24.0%	38.8%	35.5%
Lymphoma	22	49.5%	45.0%	50.0%	67.1%	19.7%	51.3%	34.6%
MM	6	65.0%	52.3%	64.7%	69.0%	40.7%	65.3%	52.8%

4.4 Quality comparison of oncology specialised *vs* general guideline developer

We compared the mean domains scores (%) of oncology specialised guideline developer (n=44) with the general guideline developer (n=9) **[Table 7].** The overall assessment score was less (33.5%) for oncology specialised developed than general guideline developer (52.8%). The applicability domain scored less (19.8%) by the specialised oncology developer concerning the general guideline developer (41.0%) of those six domains.

Table 7: *Percentage of mean domain scores of oncology vs general guideline developer.*

Domain name	Oncology Specialised Developer (n=44)	General guideline Developer (n=9)
Scope and Purpose	48.8%	66.3%
Stakeholder Involvement	40.8%	36.3%
Rigour of Development	48.7%	54.0%
Clarity of Presentation	64.8%	78.6%
Applicability	19.8%	41.0%
Editorial Independence	51.9%	46.0%
Overall Assessment	33.5%	52.8%

4.4.1 Quality assessments of oncology specialised developers

We identified five transnational societies (ESMO, NCCN, BSH, CCO and ELN) that are specialised in oncology field in developing the guidelines. The guidelines developed by CCO (n=4) obtained higher quality overall assessment score (71%) among the five societies. Whereas the guidelines (n=9) released by the BSH recorded medium overall quality score (47%). While the guidelines (n=10) published by the NCCN registered low-quality overall score (39%). Lastly, the guidelines released by the ESMO (n=17) and ELN (n=4) recorded very low overall assessment score with <20%.

We compared the quality of six domains for transnational societies. Among the six domains, we noticed the applicability domain had low-quality scores for all the five societies (<35%). Among the five societies, for editorial Independence domain CCO obtained highest quality scores (94%), while for the clarity of presentation, the rigour of development, and scope and purpose domains the CCO and BSH societies recorded high-quality scores (62%-88%). In the stakeholder involvement domain, the CCO registered high-quality score (65%), BSH obtained medium quality scores (54%) followed by low-quality scores recorded for ESMO, NCCN and ELN with less than 40%. [**Table 8]**

Table 8 *Quality of six domains for the guidelines developed by Oncology specialised developers of various transnational societies*

Society	N. Guidelines	Mean Domain scores (%)						
		Scope & Purpose	Stakeholder Involvement	Rigour of development	Clarity of presentation	Applicability	Editorial Independence	Overall Assessment
ESMO	17	40%	34%	35%	66%	16%	47%	17%
NCCN	10	38%	36%	53%	50%	28%	46%	39%
BSH	9	62%	54%	66%	81%	15%	51%	47%
CCO	4	85%	65%	86%	88%	34%	94%	71%
ELN	4	45%	28%	22%	36%	13%	48%	19%

4.4.2 Quality assessments of general guideline developers

We identified two transnational societies (AHS:7 and NICE:2 guidelines) that are specialised in developing the guidelines in oncology and other diseases. Those societies are from Canada and the UK. NICE recorded high-quality scores (>70%) in all the six domains and final overall assessment compared to the AHS of those two societies. For AHS, among the six domains, the clarity of presentation and scope of purpose domains registered high-quality scores with 80% and 64% respectively. Whereas Rigour of development domain recorded medium quality score (46%). Whilst the editorial independence and applicability domains obtained low-quality scores (<40%) followed by a very low-quality score for the stakeholder involvement (<25%). In overall, the final assessment tends to be medium quality for the AHS guidelines. **[Table 9]**

Table 9: *Quality of six domains for the guidelines developed by General guideline developers of various transnational societies.*

Society	N. Guidelines	Mean Domain scores (%)						
		Scope & Purpose	Stakeholder Involvement	Rigour of development	Clarity of presentation	Applicability	Editorial Independence	Overall Assessment
AHS	7	64%	23%	46%	80%	31%	37%	48%
NICE	2	75%	84%	83%	74%	75%	77%	71%

4.5 Overall quality assessments and clinical trial citations *(industry vs non industry)* per guideline

Table 10 shows the overall quality of 53 guidelines and the proportion of clinical trial citations (*industry vs non-industry*) per guideline. Among the guidelines published by the ESMO: MDS, CLL and CML guidelines recorded >70% of industry trial citations, but those guidelines obtained very low-quality scores. Whereas guidelines released by NCCN: CLL, CML and MM guidelines registered greater than 70% of industry trial citations and overall, the quality of these guidelines is low for CML and CLL, Medium for MM.

MDS, Myelofibrosis and primary resistant and relapsed classical Hodgkin's Lymphoma guidelines reported >70 percent of industry trial citations in the guidelines established by BSH; their quality scores were medium.

In the case of AHS, CLL and MDS documented >80% of industry trial citations, their quality of guidelines tends to be medium.

ELN published three guidelines on CML disease between 2009-2015. All three guidelines reported more than 60 percent of industry trial citations, and the quality was very low.

Table 10 *Summary of Guidelines comparing AGREE-II overall assessment score with a proportion of registered trial citations (industry vs non-industry).*

SOCIETY	GUIDELINE TITLE	YEAR	AGREE-II OVERALL ASSESSMENT SCORE	TOTAL NO OF REGISTERED TRIAL CITATIONS	REGISTERED TRIALS CITATIONS: INDUSTRY n (%)	REGISTERED TRIALS CITATIONS: NON-INDUSTRY n (%)	SPECIALITY OF DEVELOPER
European Society of Medical Oncology	CML-Diagnosis, treatment, follow-up	2012	25%	8	6(75%)	2(25%)	Oncology specialised developer
	AML-Diagnosis, treatment, follow-up	2013	17%	6	1(17%)	5(83%)	
	Myelodysplastic syndromes	2014	17%	6	6(100%)	0	
	CLL-Diagnosis, treatment, follow-up	2015	17%	4	4(100%)	0	
	Hairy cell Leukaemia	2015	17%	2	1(50%)	1(50%)	
	chronic myeloproliferative Neoplasms	2015	33%	9	4(44%)	5(56%)	
	ALL-Diagnosis, treatment, follow-up	2016	25%	15	5(33%)	10(67%)	
	waldenstroms macroglobulinemia	2013	17%	3	2(67%)	1(33%)	
	Primary cutaneous Lymphomas	2013	17%	2	1(50%)	1(50%)	
	Gastric marginal lymphoma of MALT-Type	2013	17%	1	0	1(100%)	
	Newly Diagnosed and relapsed mantle cell Lymphoma	2014	17%	10	6(60%)	4(40%)	
	Hodgkin's Lymphoma	2014	17%	6	2(33%)	4(67%)	
	peripheral T-cell Lymphomas	2015	8%	6	3(50%)	3(50%)	
	DLBCLS	2015	17%	13	5(38%)	8(62%)	
	Newly Diagnosed and relapsed Follicular Lymphoma	2016	17%	13	6(46%)	7(54%)	
	Extra nodal large B-cell lymphoma& mediastinal B-cell Lymphoma	2016	17%	6	0	6(100%)	
	Multiple Myeloma	2013	0%	5	2(40%)	3(60%)	
National comprehensive cancer network	Acute Lymphoblastic Leukaemia	2016	42%	14	9(64%)	5(36%)	General guideline Developer
	Acute Myeloid Leukaemia	2016	42%	12	0	12(100%)	
	Chronic Lymphocytic Leukaemia/ Small Lymphocytic Lymphoma	2017	33%	16	14(88%)	2(12%)	
	CML (Evidence Blocks)	2016	33%	18	13(72%)	5(28%)	

	Hodgkin Lymphoma	2017	42%	20	8(40%)	12(60%)	
	Non-Hodgkin's Lymphoma-DLBCL (Evidence Blocks)	2016	42%	18	9(50%)	9(50%)	
	Multiple Myeloma (Evidence Blocks)	2016	42%	39	28(72%)	11(28%)	
	Myelodysplastic Syndromes (Evidence Blocks)	2016	42%	11	7(64%)	4(36%)	
	Waldenstroms Macroglobulinemia/Lymphoplasmacytic Lymphoma	2016	42%	11	5(45%)	6(55%)	
	Myeloproliferative Neoplasms	2016	33%	5	3(60%)	2(40%)	
British Society of Haematology	Diagnosis and Management of Adult Myelodysplastic syndromes	2014	42%	4	4(100%)	0(0%)	Oncology Specialised developer
	Diagnosis and Management of Chronic Lymphocytic Leukaemia	2012	42%	9	4(44%)	5(56%)	
	Diagnosis and Management of Myelofibrosis	2012	42%	2	2(100%)	0(0%)	
	Management of primary resistant and relapsed classical Hodgkin's Lymphoma	2014	58%	4	3(75%)	1(25%)	
	First-line Management of Classical Hodgkin's Lymphoma	2014	50%	14	1(7%)	13(93%)	
	Management of Mantel cell Lymphoma	2012	42%	4	2(50%)	2(50%)	
	Management of Nodular Lymphocyte Predominant Hodgkin Lymphoma	2016	58%	3	1(33%)	2(67%)	
	Diagnosis and Management of Waldenstrom Macroglobulinemia	2014	33%	8	4(50%)	4(50%)	
	Guidelines for the management of Diffuse large B-cell Lymphoma	2016	58%	13	3(23%)	10(77%)	
Alberta Health Services	Management of Chronic Myeloid Leukaemia	2015	58%	19	13(68%)	6(32%)	General guideline developer
	Acute Lymphoblastic Leukaemia	2016	33%	11	4(36%)	7(64%)	
	Acute Myeloid Leukaemia	2015	50%	1	1(100%)	0(0%)	
	Chronic Lymphocytic Leukaemia	2015	50%	6	5(83%)	1(17%)	
	Lymphoma	2016	42%	14	3(21%)	11(79%)	
	Myelodysplastic syndromes	2009	50%	2	2(100%)	0(0%)	

	Multiple Myeloma	2015	50%	16	8(50%)	8(50%)	
Cancer Care Ontario	Systemic Treatment of Acute Myeloid Leukaemia	2016	67%	18	3(17%)	15(83%)	General guideline developer
	Lenalidomide in Multiple Myeloma	2012	83%	6	4(67%)	2(33%)	
	Bortezomib in Multiple myeloma	2013	67%	6	4(67%)	2(67%)	
	Management of Early-stage Hodgkin Lymphoma	2015	67%	6	0(0%)	6(100%)	
National Institute of Health care and Excellence	Non-Hodgkin's lymphoma: diagnosis and management	2016	67%	13	2(15%)	11(85%)	General guideline developer
	Myeloma: diagnosis and management	2016	75%	11	5(45%)	6(55%)	
European Leukaemia Net Foundation	CML: Management recommendations	2009	33%	8	5(63%)	3(37%)	Oncology specialised guideline developer
	CML: Management recommendations	2013	25%	19	13(68%)	6(32%)	
	CML: Management recommendations	2015	0%	8	8(100%)	0(0%)	
	Philadelphia-Negative Classical Myeloproliferative Neoplasms	2011	17%	3	1(33%)	2(67%)	

4.6 Proportions of clinical trial citation *(industry vs non-Industry)*: guidelines by disease-specific

4.6.1 Acute leukaemia's (AML and ALL) guidelines

Four guidelines were included in AML. A total of 39 recommendations were recorded, and these were associated with 37 clinical trial citations. Of these 37 citations, 5 (14%) citations were observed for industry involvement and 32 (86%) for non-industry involvement.

Higher results of non-industry citations were recorded in 3 out of 4 guidelines.

Only in AML guideline, published by ALBERTA, was observed a higher percentage of industry citations. It was recorded 100% of industry citations.

Three guidelines were identified in ALL; 39 recommendations were identified. These 39 were associated with 40 clinical trial citations: 18 were industry (45%), and 22 are non-industry (55%). Significant results of non-industry citations were registered in 2 out of 3 guidelines. Only in the guideline published by NCCN had greater than 50% of trial citations for industry involvement was observed **[Table 11]**.

Table 11: *Illustrates the total of the number of treatment recommendations, citations of registered trials (proportions of industry vs non-industry sponsored trial citations), overall AGREE-II assessment for each AML/ALL guidelines of transnational societies*

Disease	Society	No. of treatment recommendations	Registered trial Citations			Overall assessment AGREE-II
			Total	Industry n (%)	Non-Industry n (%)	
Acute myeloid leukaemia	**NCCN**	9	12	0 (0%)	12 (100%)	42%
	ALBERTA	3	1	1 (100%)	0 (0%)	50%
	ESMO	17	6	1 (17%)	5 (83%)	17%
	CCO	10	18	3 (17%)	15 (83%)	67%
	TOTAL	**39**	**37**	**5 (14%)**	**32 (86%)**	**44%**
Acute Lymphoblastic Leukemia	**ESMO**	17	15	5 (33%)	10 (67%)	25%
	NCCN	10	14	9 (64%)	5 (36%)	42%
	ALBERTA	12	11	4 (36%)	7 (64%)	33%
	TOTAL	**39**	**40**	**18 (45%)**	**22 (55%)**	**33%**

4.6.2 Myeloproliferative neoplasms (MPN) / Chronic Myeloid Leukemia (CML)

4.6.2.1 Myeloproliferative neoplasms: Four guidelines of different transnational societies were included in MPN. A total of 70 recommendations were retrieved, and these were associated with 19 clinical trial citations. Of these 19 citations, 10 citations were observed for industry involvement (53%) and 9 for non-industry involvement (47%). Significant results of industry citations greater than 50% were registered in 2 out of 4 guidelines **[Table 12].**

4.6.2.2 Chronic myeloid Leukemia: Six guidelines were identified for CML. A total of 54 recommendations were registered. These 54 were associated with 80 clinical trial citations: 58 were identified for industry (73%) and 22 for non-industry (27%). Higher results of industry citations were recorded in 6 out of 6 guidelines. No relevant percentages (>50%) was observed in non-industry citations **[Table 12].**

Table 12 *Illustrates the total number of treatment recommendations, citations of registered trials (proportions of industry vs non-industry sponsored trial citations), and overall AGREE-II assessment for each MPN/CML guidelines transnational societies.*

Disease	Society/year	No. of treatment recommendations	Registered trial Citations			Overall assessment AGREE-II
			Total	Industry n (%)	Non-Industry n (%)	
Myeloproliferative neoplasms	**NCCN**	4	5	3 (60%)	2 (40%)	33%
	ESMO	38	9	4 (44%)	5 (56%)	33%
	ELN	6	3	1 (33%)	2 (67%)	17%
	BSH	22	2	2 (100%)	0 (0%)	42%
	TOTAL	**70**	**19**	**10 (53%)**	**9 (47%)**	**31%**
Chronic myeloid Leukemia	**ESMO-2012**	5	8	6 (75%)	2 (25%)	25%
	ALBERTA-2015	9	19	13 (68%)	6 (32%)	58%
	NCCN-2016	20	18	13 (72%)	5 (28%)	33%
	ELN-2009	8	8	5 (63%)	3 (37%)	33%
	ELN-2013	9	19	13 (68%)	6 (32%)	25%
	ELN-2015	3	8	8 (100%)	0 (0%)	0%
	TOTAL	**54**	**80**	**58 (73%)**	**22 (27%)**	**29%**

4.6.3 Myelodysplastic syndromes Guidelines

Four guidelines were included in MDS that are developed by ESMO, NCCN, ALBERTA and BSH. A total of 75 recommendations were recorded, and these were associated with 23 clinical trial citations. Of these 23 citations, 19 citations were observed for industry involvement (83%) and 4 others for non-industry involvement (17%). Higher results of industry citations were recorded in 4 out of 4 guidelines. Guidelines published by ESMO, ALBERTA and BSH was observed a higher percentage of the industry citation. It was recorded 100% of industry citations **[Table 13].**

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Table 13 *Demonstrates the total number of treatment recommendations, citations of registered trials (proportions of industry vs non-industry sponsored trial citations), and overall AGREE-II assessment for each Myelodysplastic syndromes Guidelines of transnational societies.*

Society	No. of treatment recommendations	Registered trial Citations			Overall assessment AGREE-II
		Total	Industry (%)	Non-Industry (%)	
ESMO	24	6	6 (100%)	0 (0%)	17%
NCCN	7	11	7 (64%)	4 (36%)	42%
ALBERTA	6	2	2 (100%)	0 (0%)	50%
BSH	38	4	4 (100%)	0 (0%)	42%
TOTAL	**75**	**23**	**19 (83%)**	**4 (17%)**	**38%**

4.6.4 Chronic Lymphocytic Leukemia Guidelines

Four guidelines were identified for CLL disease. 72 recommendations were retrieved, and these were associated with 35 clinical trial citations: 27 citations were observed for the industry involvement (77%) and other 8 for non-industry involvement (23%). In 3 out of 4 guidelines, significant results for industry citations were reported. Greater than fifty percent of non-industry citations were registered only in the CLL guidelines released by BSH. Compared to 44% of industry citations, 56% of non-industry citations were registered. The quality for 3 out of 4 guidelines recorded less than 50% of the overall assessment score. The average quality of four CLL guidelines was 36% **[Table 14]**.

Table 14 *Shows the total number of treatment recommendations, citations of registered trials (proportions of industry vs non-industry sponsored trial citations), and overall AGREE-II assessment for each Chronic Lymphocytic Leukemia Guidelines of transnational societies.*

Society	No. of treatment recommendations	Registered trial Citations			Overall assessment AGREE-II
		Total	**Industry (%)**	**Non-Industry (%)**	
ALBERTA	11	6	5 (83%)	1 (17%)	50%
BSH	29	9	4 (44%)	5 (56%)	42%
ESMO	7	4	4 (100%)	0 (0%)	17%
NCCN	25	16	14 (88%)	2 (12%)	33%
TOTAL	**72**	**35**	**27 (77%)**	**8 (23%)**	**36%**

4.6.5 Lymphoma Guidelines

We identified 22 guidelines (6 HL, 1 HCL, 15 NHL) of different societies. The total number of treatment recommendations were 502. The total number of citations of registered trials 190. Of those 35% (n=67) industry and 65% (n=123) non-industry. The average quality of 22 lymphoma guidelines was 35% **[Table 15]**

Table 15 *Shows the total number of treatment recommendations, citations of registered trials (proportions of industry vs non-industry sponsored trial citations), and overall AGREE-II assessment for each Lymphoma Guidelines.*

Disease	Society	No. of treatment recommendations	Registered trial Citations			Overall assessment AGREE-II
			Total	**Industry (%)**	**Non-Industry (%)**	
Hodgkin's Lymphoma	NCCN	41	20	8 (40%)	12 (60%)	42%
	ESMO	17	6	2 (33%)	4 (67%)	17%
First-line management of classical Hodgkin's Lymphoma	BSH	24	14	1 (7%)	13 (93%)	50%
Management of primary resistant and relapsed classical Hodgkin's Lymphoma		21	4	3 (75%)	1 (25%)	58%
Management of Nodular lymphocyte-predominant Hodgkin's Lymphoma		24	3	1 (33%)	2 (67%)	58%

Disease	Society	No. of treatment recommendations	Registered trial Citations			Overall assessment AGREE-II
			Total	Industry (%)	Non-Industry (%)	
Management of Early-stage Hodgkin's Lymphoma Diffuse large B-cell Lymphoma	CCO	8	6	0 (0%)	6 (100%)	67%
Diffuse large B-cell Lymphoma	NCCN	18	18	9 (50%)	9 (50%)	42%
	ESMO	32	13	5 (38%)	8 (62%)	17%
	BSH	28	13	3 (23%)	10 (77%)	58%
Lymphoma	ALBERTA	61	14	3 (21%)	11 (79%)	42%
Non-Hodgkin's Lymphoma	NICE	14	13	2 (15%)	11 (85%)	67%
Waldenstrom Macroglobulinemia	NCCN	23	11	5 (45%)	6 (55%)	42%
	ESMO	8	3	2 (67%)	1 (33%)	17%
	BSH	25	8	4 (50%)	4 (50%)	33%
Mantel cell Lymphoma	ESMO	18	10	6 (60%)	4 (40%)	17%
	BSH	19	4	2 (50%)	2 (50%)	42%
Newly Diagnosed and relapsed mantle cell Lymphoma	ESMO	19	13	6 (46%)	7 (54%)	17%
Peripheral T-cell Lymphomas		15	6	3 (50%)	3 (50%)	8%
Primary cutaneous Lymphomas		13	2	1 (50%)	1 (50%)	17%
Gastric marginal lymphoma of MALT-Type		5	1	0 (0%)	1 (100%)	17%
Extra nodal diffuse large B-cell lymphoma & primary mediastinal B-cell Lymphoma		34	6	0 (0%)	6 (100%)	17%
Hairy cell Leukemia		35	2	1 (50%)	1 (50%)	17%
Total		**502**	**190**	**67 (35%)**	**123 (65%)**	**35%**

4.6.6 Multiple Myeloma Guidelines

Six guidelines were identified in Multiple Myeloma disease. 76 recommendations were retrieved, and these were associated with 83 clinical trial citations: 51 citations were recorded for industry involvement (61%) and other 32 for non-industry involvement (39%). Higher results of industry citations were observed in 3 out of 6 guidelines. Only in MM guidelines, published by NICE, it was observed >50% of non-industry citations. The average quality of the six guidelines was recorded greater than fifty per cent **[Table 16]**

Table 16 *Demonstrates the total number of treatment recommendations, citations of registered trials (proportions of industry vs non-industry sponsored trial citations), and overall AGREE-II assessment for each Multiple Myeloma Guideline of various transnational societies.*

Society/year	No. of treatment recommendations	Registered trial Citations			Overall assessment AGREE-II
		Total	Industry (%)	Non-Industry (%)	
ESMO	7	5	2 (40%)	3 (60%)	0%
ALBERTA	11	16	8 (50%)	8 (50%)	50%
NCCN	35	39	28 (72%)	11 (28%)	42%
CCO-2012	7	6	4 (67%)	2 (33%)	83%
CCO-2013	6	6	4 (67%)	2 (33%)	67%
NICE	10	11	5 (45%)	6 (55%)	75%
TOTAL	**76**	**83**	**51(61%)**	**32(39%)**	**53%**

4.7 Summary: Proportion of clinical trials citations (*industry vs non-industry*)

For 53 guidelines, we retrieved 927 treat recommendations those were associated with 507 trial citations. Of those 507, 50.3% (n=255) trial citations were observed for the industry involvement and 49.7% (n=252) for the non-industry involvement. >50% percentages of industry funded trial citations were recorded in MDS (82.6%), CLL (77.1%), CML (72.5%), MM (61.4%) and MPN (52.6%) guidelines, respectively. Lower percentages of industry funded trial citations were recorded in ALL with 45%, Lymphoma 35.3% followed by AML 13.5% **[Table 17]**.

Table 17 *Illustrates the total number of guidelines, treatment recommendations, citations of registered trials (proportions of industry vs non-industry sponsored trial citations) for each disease group.*

Disease	No. of guidelines	No. of treatment recommendations	Registered trial Citations		
			Total	Industry (%)	Non-Industry (%)
AML	4	39	37	5 (13.5%)	32 (86.5%)
ALL	3	39	40	18 (45.0%)	22 (55.0%)
MPN	4	70	19	10 (52.6%)	9 (47.4%)
CML	6	54	80	58 (72.5%)	22 (27.5%)
MDS	4	75	23	19 (82.6%)	4 (17.4%)
CLL	4	72	35	27 (77.1%)	8 (22.9%)
Lymphoma	22	502	190	67 (35.3%)	123 (64.7%)
MM	6	76	83	51 (61.4%)	32 (38.6%)
Total	**53**	**927**	**507**	**255 (50.3%)**	**252 (49.7%)**

4.8 Summary: proportions of registered trials (*industry vs non-Industry*) after the duplicate trial citations

After removing duplicate trial citations, 327 trials were recorded for 53 leukaemia, Lymphoma, and Multiple myeloma guidelines. Of those 327 trials, 48.6% (n=159) were industry-sponsored and 51.4% (n=168) non-industry sponsored trials. Significant percentages of clinical trials were funded by industry have been registered in MDS (72.2%), CLL (69.2%), MM (64.8%), CML (64.5%) and for MPN guidelines with 57.1%, respectively. The higher percentage of Clinical trials funded by non-industry were observed in AML (83.3%), lymphoma (63.5%) guidelines concerning industry-sponsored trials **[Table 18].**

Table 18 *Demonstrates the proportion of registered trials (Industry vs Non-Industry) after removing duplicate citations for 53 Leukemia, Lymphoma, and Multiple myeloma guidelines for each disease-specific.*

Disease	N. Guidelines	N. Treatment recommendations	N. Registered trials	Industry n (%)	Non-Industry n (%)
AML	4	39	30	5 (16.7%)	25 (83.3%)
ALL	3	39	28	14 (50.0%)	14 (50.0%)
MPN	4	70	14	8 (57.1%)	6 (42.9%)
CML	6	54	31	20 (64.5%)	11 (35.5%)
MDS	4	75	18	13 (72.2%)	5 (27.8%)
CLL	4	72	26	18 (69.2%)	8 (30.8%)
LYMPHOMA	22	502	126	46 (36.5%)	80 (63.5%)
MM	6	76	54	35 (64.8%)	19 (35.2%)
TOTAL	**53**	**927**	**327**	**159 (48.6%)**	**168 (51.4%)**

4.9 Comparison of guidelines overall quality and proportions of clinical trial citations (*industry vs non-industry*) for transnational societies

We analysed seven transnational societies. Of those seven, ELN registered higher proportions of industry-sponsored trial citations when compared to non-industry, but the overall quality tends to be very low. The guidelines released by the CCO, NICE and BSH had cited lower percentage of clinical trial citations that are sponsored by the industry, and the overall quality is greater than 70% for CCO and NICE while BSH had medium quality scores (47%). In the guidelines published by the NCCN and AHS, we noticed with greater than 50% industry clinical trials citations, but their overall quality scores are medium and low. The guidelines developed by the ESMO 47% of industry trial citations were recorded, and the overall quality scores are very low **[Table 19]**.

***Table 19**: Proportion of registered trial citations used to make recommendations in various transnational societies' guidelines.*

Society	N. Guidelines	Disease types	N. Registered trials citations	Industry n (%)	Non-Industry n (%)	Overall quality Assessment Score (AGREE-II)
ESMO	17	Leukemia, Lymphoma, Multiple myeloma	115	54 (47.0%)	61 (53.0%)	17%
NCCN	10	Leukemia, Lymphoma, Multiple myeloma	164	96 (58.5%)	68 (41.5%)	39%
AHS	7	Leukemia, Lymphoma, Multiple myeloma	69	36 (52.2%)	33 (47.8%)	48%
CCO	4	Leukemia, Lymphoma, Multiple myeloma	36	11 (30.6%)	25 (69.4%)	71%
NICE	2	Lymphoma, Multiple myeloma	24	7 (29.2%)	17 (70.8%)	71%
ELN	4	Leukemia	38	27 (71.1%)	11 (28.9%)	19%
BSH	9	Leukemia, Lymphoma	61	24 (39.3%)	37 (60.7%)	47%

5.) DISCUSSION

5.1 Discussion

Clinical practice guidelines play a critical role in health care, and they are the most widely utilized as a clinical reference. In 2004 the International Committee of Medical Journal Editors (ICMJE) made registration a condition for publication in 11 leading medical journals.[126] In our research, we found that we could not find the trial registry details for certain trials conducted after 2004, which are published in a medical journal. It is uncertain if those studies have been registered.

The Institute of Medicine (IOM) proposed in 2009 that the groups that produce CPG should typically exclude individuals with COI as panel members and should not accept direct support from pharmaceutical companies or corporate foundations for the creation of CPG. Development organizations should report their COI and procedures in the guidelines, which are the indirect funding source to source the guidelines. If no experts without a conflict of interest can be found on any topic, those involved should be allowed to participate in background discussions, but not in creating and drafting specific recommendations or their adoption by vote.[2] While the IOM recommended excluding the personnel with COI and the people who received direct funding from Industry; we observed that ELN's guidelines had included the expert with COI in the guideline development group.

Clinical practice guidelines need to have a scientific rigour and devoid of a perceived conflict of interest.[127] The necessity of high quality and unbiased guidelines is very important to provide better clinical care. During the last two decades, there was an increasing prevalence of industry sponsorship in a clinical drug trial.

Our study identified industry funding in 50.3% of the haematological clinical trial citations. This data follows the tendency in other fields of medicine. Indeed, studies of general medical journals have revealed rates of 40-60%.[128,129]

The prevalence of pharmaceutical industry sponsorship can negatively influence the trial's development in different points: from the study design, results in an outcome, and publication results.[130]

The findings of a clinical drug trial sponsored by a pharmaceutical firm or whose perpetrator has a financial conflict of interest are much more often beneficial to the sponsoring company drugs than trials financed by other sources.

Conflict of interest is consequential to industry sponsorship in the medical practice: a physician who receives industry payments are twice as likely to recommend brand-name drug and may also assess clinical trial more favourably than physicians without industry affiliation. One study of >279,000 physicians including internal medicine, family medicine, cardiology and other specialities found that industry-sponsored meals were associated with increased rates of prescribing the promoted brand name medication.[131]

Kasselheim et al. reported an increasing physicians' scepticism about industry-funded research affected their responses to high rigour and low-rigour trials.[132]

Although the pharmaceutical industry has supported many major drug trials that have been of particular clinical importance,[133] Industry-sponsored influence trials may be more than hypothetical: industry-sponsored trial may be more likely to report favourable outcome, the influence of study design or publication bias.[130]

According to *Kasselheim et al,* "excessive scepticism about industry-supported trials could impede the proper translation of findings into practice."[132] One study of a biomedical journal reported that after publishing the results of a large, well-designed trial describing a new use for a widely prescribed class of drugs, many of its readers believed that the trial results did not justify a change in clinical management. They cited industry funding as a key reason for this conclusion.[134]

Although scepticism is a potential source of bias, it can reduce the credibility and acceptance of even high-quality research that is industry supported. Our study reported a proportional correlation between overall low-quality guidelines and the presence of industry-sponsored clinical trial. For instance, in PTCL guideline published by ESMO society, we recorded 50% of industry sponsorship while the overall quality is 8%; in CLL guideline published by ESMO society, we registered 77% of industry sponsorship overall quality assessment of 17%.

Another crucial point is publication bias, from the selective publication of positive results or withholding of negative findings. The predominance of positive results in studies funded by pharmaceutical companies with the help of ghostwriters. Several aspects about the influence of pharmaceutical industries on the results and publication of drug trials have not been systematically investigated.[15,16]

Richard Smith, a long-serving editor of the *British Medical Journal*, focused the fact that many medical journals received a substantial income from the pharmaceutical companies, from

advertisements and reprints. He recognized therein as a risk to journals' independence and postulated that they often serve as extensions of pharmaceutical companies' marketing departments. Medical journals should therefore publish their income regularly.[135]

In conclusion, industry sponsorship may influence negatively results in an outcome. So, new strategies to ensure the quality of the clinical trial and stronger policies about journal transparency are necessary to improve the quality of guidelines in the hemato-oncology field and other medical areas.

Limitations of the study:

Some published trials used to make recommendations in CPGs failed to cite the trial identifiers in the publication not to identify the sponsor for those studies.

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6.) ABBREVIATIONS

LIST OF ABBREVIATION AND ACRONYMS

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
AHS	Alberta Health Services
ASCO	American Society of Clinical Oncology
AGREE	Appraisal of Guidelines for Research and Evolution
BCL	B-cell lymphoma
BSH	British Society of Hematology
CCO	Cancer Care Ontario
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
CTRI	Clinical Trials Registry – India
DLBCL	Diffuse Large B-cell Lymphoma
ELN	European Leukemia Net
ESMO	European Society of Medical Oncology
Extra nodal DLBCL	Extra nodal Diffuse Large B-cell Lymphoma
FL	Follicular Lymphoma
FDAMA	Food and Drug Administration Modernization Act
HCL	Hairy Cell Lymphoma
HL	Hodgkin's Lymphoma
ICMR	Indian Council of Medical Research
ICTRP	International Clinical Trials Registry Platform
ICMJE	International Committee of Medical Journal Editors
MCL	Mantle Cell Lymphoma
MDS	Myelodysplastic Syndrome
MPN	Myeloproliferative Neoplasm
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute of Health
NLPHL	Nodular lymphocyte-predominant Hodgkin lymphoma
NHL	Non-Hodgkin's Lymphoma
PTL	Peripheral T-cell Lymphomas
PCL	Primary Cutaneous lymphomas
TCL	T-cell lymphomas
WM	Waldenstrom's macroglobulinemia
WHO	World Health Organizzation

7.) PUBLICATIONS

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The efficacy of fasting regimens on health outcomes: a systematic overview

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Abstract

Introduction: Fasting can be defined as abstinence or reduction from food, drink, or both, for a defined period. There are many different types of fasting regimens, such as Ramadan fasting, Intermittent fasting, Christian Orthodox fasting. The aim of this overview is to provide an exhaustive summary on the beneficial effects and harms associated with fasting regimens and discuss mechanisms by which this non - pharmacological approach might lead to improve human health.

Evidence acquisition: A systematic search was performed on MEDLINE (PubMed), Embase, Cochrane Library and CINHAL. We included systematic reviews (SRs) that report on impact of different types of fasting regimens on health. Selection of SRs, data extraction and quality assessment were undertaken in duplicate.

Evidence synthesis: A total of 21 SRs were included. Cumulatively, 97 health outcomes were identified. Of them, cardiovascular risk factors were the most frequently analyzed. Ramadan fasting is associated with significant improvements in body weight and visceral lean mass, high-density lipoprotein cholesterol (HDL-c), and with reductions in low-density lipoprotein cholesterol (LDL-c) and total cholesterol (T-chol), especially in cardiac patients. Similarly, reviews on Intermittent and Orthodox fasting proved benefits of those on weight, BMI, lipidic and glucose profile, inflammatory markers.

Conclusions: Fasting regimens showed potential beneficial effects on several health indicators in adult populations. Nevertheless, evidence on some specific health dimensions (cognitive function, well-being, quality of life) is limited. Thus, in the future, further RCTs or cohort studies with good methodological quality and larger sample sizes are warranted to better understand the underlying biological mechanism and the benefits on multidimensional aspects of health.

Key words: Ramadan fasting - Intermittent fasting - Christian Orthodox fasting – health outcomes – overview – systematic review

The efficacy of fasting regimens on health outcomes: A systematic overview

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INTRODUCTION

Practiced since ancient times, fasting is a nutritional dietary pattern defined by partial or total abstinence from solid food and drinks with a little or no daily caloric intake for a defined and restricted period.

According to recent evidences, fasting could represent a promising non-pharmacological intervention able to improve health, increase longevity and control several chronic diseases and health problems. [1–3] For this reason, there is a widespread interest regarding the health implications of this dietary intervention.

The most studied fasting strategies are intermittent fasting (IF) and religious fasting (e.g., Ramadan fasting and Christian Orthodox fasting). While religious fasting is carried out for spiritual purposes and it is not clearly based on evidences [4,5] , therapeutic fasting (e.g. complete alternate-day fasting, time-restricted feeding, caloric restriction, etc.) are medical interventions aimed to reduce energy intake and metabolic expenditure [6].

In vivo studies have shown that rodents and mice keon a fasting diet and on caloric restriction display a significant increase in life expectancy and a reduction of the incidence and prevalence of a considerable number of age-related chronic diseases (e.g., cancer, diabetes, cardiovascular disease etc.) [7–10]. In animal models, the reduction in chronic disease incidence and prevalence is mainly explained by a large series of complex events, including stress response, autophagy, apoptosis, and modification in homeostasis balance, all triggered by a food-deprived/fasted. Despite mounting evidence supporting the feasibility, safety and beneficial effects of fasting in animal models, data on its potential benefits on health outcomes and complex biological mechanisms in humans are incomplete.[11] Indeed, it’s still unknown whether fasting is safe and functional because of inconsistent and discordant findings from previous SRs and meta-analysis.

To date, there are still no systematic overviews assessing the risk/balance of fasting and its transferability into clinical practice.

In this regard, the main goal of this overview is to provide an exhaustive summary of the available evidence on the potential beneficial effects and harms associated with the most common fasting regimens and discuss mechanisms by which this non - pharmacological approach might lead to improve human health. Furthermore, our secondary purpose is to identify needs, uncertainties and priorities for future systematic reviews to provide more specific information to patients, clinicians and policy makers.

MATERIALS AND METHODS

An overview of systematic reviews (SRs) on the potential beneficial impact on health of the most practiced regimens of fasting was conducted. The final report was written according to the *Cochrane Handbook for Systematic Reviews of Interventions.*

2.1 Eligibility Criteria

SRs were selected for inclusion in this overview according to the following eligibility criteria:
Population: Eligible participants were healthy people or subjects with a prevalent diagnosis of disease who had sought medical attention at study entry.
Interventions: Religious or therapeutic fasting with a reduction of daily caloric intake measured in Kcal/die;
Studies: the overview included systematic reviews reporting on the associations between fasting dietary patterns and health outcomes. An SR was selected if it included at least one randomized controlled trial (RCT) or one observational study, had clinically relevant health outcomes, and reported clear and strong eligibility criteria for identified studies;
Outcomes: indicators of the overall dimensions of health status, according to the 1948 WHO definition of health concept;
Period: papers published from January 1st, 1980 to March 31st, 2019;
Setting: any type of setting, without any limitation;
Language: English, Italian.

2.2 Search strategy

For the purpose of our study, databases from Medline (PubMed), Embase, CINHAL Complete and Cochrane Library were consulted. The literary search was conducted by two reviewers (AS and MF) with all conflicts and disagreements resolved through discussion with a third author (DC) expert in methodology and epidemiology. In order to identify potentially relevant papers, we used a broad strategy combining Mesh terms: “fasting”, “alternate day fasting”, “intermittent fasting”, “Ramadan fasting”, “human”, “Christian Orthodox fasting” with specific keywords. We launched on search databases three strings, one for each of the three studied fasting regimens. The databases were consulted on March 2019. We decided to restrict our search to articles written in English or Italian. Other potential eligible studies were identified with a snowballing approach by screening the reference lists in all selected papers.

2.3 Selection of studies

Records emerging from our search strategy were collected in an Excel spreadsheet. After removing duplicates, two overview authors (AS and MF) independently assessed titles and abstracts of potential eligible studies. Lastly, the selected papers were reviewed by reading full texts. The authors recorded all steps of studies selection process in a flow chart, documenting also reasons of papers exclusion. Disagreements and discordances were resolved by consensus or discussion with the third party (PAB) and in the wider team when necessary (MP, PAB,NP).

2.4 Data extraction and management

Information from the selected SR were transferred by two overview authors (AS and MF) into a predefined extraction form database, which was controlled and double-checked by a third reviewer (DC) in order to correct any error in data extraction, entry and management. For each included SR, we collected the following information: author, year, number and typology of the studies included in the SR, number of participants included in the SR, description of results with data. We presented collected data in Table S2 Characteristics of the studies and in Table S3 of results.

2.5 Assessment of methodological quality of included reviews

The methodological quality of the reviews included in our overview was evaluated using the AMSTAR tool in order to assess the potential presence of bias in the review process of each selected SR and quantify its impact on the reported effect estimates. [12–14]. Two overview authors (MF and AS) analyzed the included papers in blind and discordances were documented and resolved by discussion between the reviewers and in wider team when necessary. We did not re-assess the quality of the randomized controlled trials (RCTs) or observational studies included in potentially eligible SRs.

2.6 Prioritization of study findings

We selected as *primary/major outcomes* all risk factors for diseases (e.g. anthropometric body measures, cardiovascular risk factors, etc..) and as *secondary/minor measures* well-being, quality of life, mood and mental disorders and nutritional and dietary parameters.

2.7 Data synthesis

As a result of a preliminary qualitative assessment of study findings and efficacy trials of the three fasting regimens analyzed (i.e., Ramadan fasting, Christian Orthodox fasting, Intermittent fasting), we combined and summarized the main findings of the included SR in a narrative summary, by categorizing them within the following framework, organized by health status of enrolled participants. Specifically, the overview authors, supported by experts in nutrition, decided to report in the final paper the study results without listing them by single dietary intervention. Furthermore, we ascertained and discussed limitations in the evidence base, including overall methodological quality of the identified reviews, and this informed recommendations for future research.

RESULTS

3.1 Description of studies

A total of 21 SRs matched the inclusion criteria and were included in this systematic overview. Our search on PubMed, Embase, Cinhal Complete and Cochrane Library provided a total of 5,239 records. After removing duplicates, 3,688 records remained. Of these, 2,170 were excluded according to title and abstract due to their inconsistency with the inclusion criteria. Subsequently, 1,518 full texts were read, and 1,497 were excluded. The main reason for excluding full-text articles was the study design. The selection process was summarized in a PRISMA flow-chart (Fig. 1). The full list of studies included can be found in Annex S1.

In detail, 5 reviews included RCTs, the others contained cohort studies. The dates of searches in the reviews ranged from 2012 to February 2019. Of the 543 studies included in the selected SRs, only a minor part enrolled child or adolescent.

3.2 Methodological quality of included systematic reviews

The methodological quality of the included reviews (Table 1) showed a remarkable number of problems with selection and critical methodological assessment. Among the 21 included SRs, only one reporting on the impact of Ramadan fasting had significant methodological limitations- The other 20 selected reviews present minor limitations. While few reviews present some limits regarding with the comprehensiveness of the search, most included SRs showed some weaknesses in relation to study selection and to the analysis of the emerged evidence.

3.3 Narrative synthesis of results

We observed heterogeneous and various study findings. Cumulatively, 97 health outcomes were identified. Of them, cardiovascular risk factors were the most frequently analyzed and ascertained; the identified papers report 33 observations about this health variable. Other study findings were renal diseases (12 outcomes), gastro-intestinal diseases (8 outcomes), inflammation and oxidative stress (12 outcomes) and dietary and nutritional aspects. Infectious diseases (7 outcomes) were measured less frequently by few studies. Well-being, quality of life and mood disorders were not assessed in any identified SR. We report the characteristics of the studies included in the annexed Table S2. A short narrative synthesis is presented in the annexed S3 Table of results. Herein, we report the most significant emerged results, organized by health status of participants.

3.3.1 Effects of fasting on outcomes of disease

In total, 9 SR evaluated the effect of fasting regimens as a non-pharmacological management of illnesses. Study findings were discordant; while relevant improvements were found in 23 of the 97 identified outcomes, the selected studies showed a negative or not significant impact of this dietary intervention on the other health measures.

3.3.1.2 Cardiovascular risk factors

Some SRs were conducted with a view to discuss the impact of Ramadan fasting on incidence of cardiovascular disease and lipid profile of patients diagnosed with a stable cardiac disease. Fasting did not appear to bring changes in incidence of acute cardiac illness during Ramadan fasting [15] Nevertheless, Ramadan fasting is associated with significant improvements in high-density lipoprotein cholesterol (HDL-c), and reductions in low-density lipoprotein cholesterol (LDL-c) and total cholesterol (T-chol) in cardiac patients. One SR assessed the effect of fasting regimens on subjects with a prevalent diagnosis of cardiac disease who had sought medical attention at study entry. Therapeutic fasting restriction appears an effective non-pharmacological therapy for weight loss. In particular, fasting groups showed relevant decreases in body weight [15]

3.3.1.3 Kidney diseases

Bragazzi analyzed correlation between fasting and kidney diseases. Ramadan fasting did not appear to decrease health outcomes in patients with a diagnosis of renal colic in a statistically significant and clinically relevant way and no injurious effect of this fasting intervention for the renal graft function was shown in renal transplant recipients. Furthermore, regarding the effect of Ramadan on patients with chronic kidney disease (CKD), no severe adverse effects and no statically significant change of glomerular filtration rate (MD 0.00 ± 0.098, 95% CI −0.19 to 0.19, t=0.02, P=0.99, I2=0.00%) have been reported by the included meta – analysis [17].

3.3.1.4 Digestive disorders

Only one SR reported data on digestive disorders as health outcomes in patients diagnosed with chronic peptic ulcer diseases, duodenal ulcer and inflammatory bowel under pharmacological treatment [18]. Ramadan fasting appeared to raise and increase peptic ulcer complications (e.g. perforation, bleeding). The deteriorating impact was significant only on patients diagnosed with peptic ulcers on therapy. Results for risk acute appendicitis and peptic ulcer diseases are uncertain and discordant. Nevertheless, fasting appeared to increase incidence of acute mesenteric ischemia, hyperemesis gravidarum and primary small bowel volvulus. Lastly, fasting did not bring serious and relevant risks on patients affected by an inflammatory bowel.

3.3.1.5 Infectious diseases

Bragazzi conducted a SR on the clinical impact of Ramadan fasting on patients with infectious diseases. This dietary pattern has a scarce impact on clinical signs and symptoms of diarrheal patients and a protective effect on urinary tract infections in urological patients. Furthermore, regarding the impact of Ramadan on patients with HIV, the author didn't report any change in treatment adherence and compliance, diarrhea, CD4 cell count, viral load, hematocrit level, kidney, liver function, and lipid profile [19].

3.3.1.6 Inflammation

One identified review assessed the influence of Ramadan fasting on immune system regulation in patients with stable cardiac illnesses, asthma and psychiatric disorders (schizophrenia). The selected paper showed the safety of the dietary intervention and its beneficial effects on oxidative stress in all recruited patients [16].

3.5.1.7 Hormonal and metabolic homeostasis

Two SRs reported data on the potential beneficial effect of fasting on hormonal and metabolic homeostasis in pre-diabetes and obese patients [20,21]. Intermittent fasting (IF) and alternate day fasting (ADF) bring decreases in glucose serum concentrations (3%–6% from baseline) and in fasting insulin levels that were reduced by 20%–31% after 8–12 weeks of IF and ADF. Reliable increases in insulin sensitivity were also found. [20]. Similar metabolic improvements were reported by a meta- analysis that showed better insulin serum concentrations induced by intermittent fasting regimens (WMD: - 4.66 pmol/ l - 9.12 pmol/l to - 0.19 pmol/l; p< 0.041).

3.5.2 Effects of fasting on healthy participants

In total, 15 SRs reported data on impact of fasting regimens in healthy recruited participants. Study findings were discordant; while relevant improvements were found in 31 of the 97 identified outcomes, the selected studies showed a negative or not significant impact of this dietary intervention on the other health measures.

3.5.2.1 Anthropometric body measurements

Several included papers analyzed the correlation between studied fasting regimens and anthropometric measurements. Two meta-analysis, conducted in order to ascertain the impact of Ramadan fasting on body composition in healthy population, reported a weight loss statistically significant in enrolled males (SMD = -0.24, 95 % CI = -0.36, -0.12, p = 0.001), but not in women (SMD = -0.04, 95 % CI = -0.20, 0.12). While no change in fat percentage between pre-Ramadan and post-Ramadan in people with normal weight (-0.41 (-1.45 to 0.63) %, p = 0.436) was reported, on the other hand loss of fat-free mass was significant between pre-Ramadan and post-Ramadan, but was about 30% less than loss of absolute fat mass.[22]. These finding were momentary; indeed, after the end of Ramadan, there was a return to pre-Ramadan values. Evidence of similar beneficial effects on anthropometric body composition measurements were found in SRs and meta-analysis reporting on the effectiveness of intermittent fasting on weight loss [23]. One quantitative meta-analytic analysis showed that the pooled change in body weight, fat mass and fat-free mass was 4.30 kg (95% CI: 3.41, 5.20), 4.06 kg (95% CI: 2.99, 5.13) and 0.72 kg (95% CI: -0.07, 1.51), respectively. By contrast, the

overall impact of Christian Orthodox fasting (COF) on body weight is still unclear because of conflicting results [24]

3.5.2.2 Cardiovascular risk factors

One included meta-analysis showed a reduction in low-density lipoprotein serum levels (SMD = -1.67, 95 % CI = -2.48 to -0.86) and fasting blood in both sex groups compared to levels prior to Ramadan [25]. Furthermore, in males, Ramadan fasting determined a significant reduction in total cholesterol (SMD = -0.44, 95 % CI = -0.77 to -0.11) and LDL levels (SMD = -2.22, 95 % CI = -3.47 to -0.96) and a small decrease in triglyceride levels (SMD = -0.35, 95 % CI = -0.67 to -0.02) were reported. Similar improvements in lipid profile were found in SRs conducted in order to discuss and analyse health effects induced by COF and IF regimens. [20-23]. In particular, the overall impact of OF on lipids serum concentration appears to be optimal, with a demonstrated consistent decrease of total cholesterol and LDL-C levels. Lastly, regarding the effect of fasting on the incidence of cardiovascular diseases, this dietary intervention did not appear to bring changes in incidence of acute cardiac illness during Ramadan fasting [28].

3.5.2.3 Inflammation

A selected SR and meta-analysis evaluated the potential beneficial influence of Ramadan fasting on immune system regulation. Diurnal fasting resulted in small reductions in IL-1 (Hedge's $g = 0.016$), CRP/hs-CRP (Hedge's $g = 0.119$), MDA (Hedge's $g = 0.219$), TNF-α (Hedge's $g = 0.371$) and IL-6 (Hedge's $g = 0.407$), suggesting a possible protection against inflammation and oxidative stress [29].

3.5.2.4 Pregnancy

Glazier performed a SR and meta-analysis on the effect of Ramadan fasting during pregnancy on perinatal outcomes in pregnant Muslim women. The most relevant results emerged from this meta-analysis was represented by decrease in placental weight in fasting pregnant mothers (SMD -0.94, 95% CI -0.97 to -0.90), although this data was supported by a single observational study. No data was reported for perinatal mortality [30].

3.5.2.5 Hormonal and metabolic homeostasis

Three included papers analyzed the correlation between studied fasting regimens and hormonal and metabolic outcomes. One meta-analysis, conducted in order to find out the influence of Ramadan fasting on health outcomes in enrolled participants, reported a reduction of fasting blood glucose serum concentrations (SMD = -1.10, 95 % CI = -1.62 to -0.58), compared to levels prior to Ramadan, that can be explained by changes in body weight and composition. [25]. Similar improvements were also observed in healthy subjects after an intermittent fasting period, as shown in another meta-analysis that reported a significant reduction in insulin (SDM −1.019; 95% CI −1.362, −0.675 p<0.000) and IGF-1 levels (SDM −0.546; 95% CI −0.750, −0.342 p<0.000) [31]. Furthermore, relevant increases in insulin sensitivity had been shown in fasting subjects; indeed, Lettieri Barbato found a significant reduction in the HOMA Index after the dietary intervention (SDM −0.837; 95% CI −0.990, −0.750 p<0.000)

DISCUSSION

This systematic overview was conducted to provide a comprehensive and exhaustive update of current available literature on the association between fasting and health outcomes in the general population.

CR is a dietary pattern defined by a reduction in daily caloric intake, without any deficiency of essential nutrients. Numerous in vivo and in vitro studies proved a robust correlation between CR and the increase in life span. Good evidence of this can be demonstrated by an increase in life expectancy both in animal [11,12] and human models. Furthermore, previous experimental and observational studies have confirmed a significant reduction in the incidence of many non – communicable diseases [13,14] in animals and humans kept on a CR diet. Indeed, reducing the average daily caloric intake prompts complex biological and chemical mechanisms that can contribute to the benefits.

Previous SRs have evaluated the potential beneficial impact of fasting on single and specific health predictors; on the other hand, this review was focused on summarizing all findings on this topic with a view to draw more definite conclusions about the safety and efficacy of fasting. Our search identified 21 SRs reporting data from 543 RCTs and observational studies. In this overview, we have placed emphasis upon the three most widely studied fasting interventions (Ramadan fasting, Christian Orthodox Fasting and Intermittent fasting).

Fasting seems to lead to encouraging changes in healthy or ill subjects in a remarkable number of health dimensions (e.g. anthropometric body composition measurements, inflammation,

cardiovascular risk factors, insulin sensitivity, incidence of acute cardiac illnesses, etc..), that were all considered to be strong surrogates of longevity and successful or healthy ageing.

The most consistent results were represented by reduction in body measurements (e.g. body weight and visceral lean mass) and cardiovascular risk factors (e.g. lipidic profile, blood pressure). A large part of included SRs showed a significant weight loss and improvements in lipidic profile after a limited period of fasting, in both people diagnosed with stable cardiac diseases and healthy participants. [21,25]. Nevertheless, those benefits would not be lasting. Indeed, after the end of Ramadan, there was a return to pre-Ramadan weight. This could be partially explained by the fact that protracted periods of food deprivation and reduction could be followed by phases of overeating at food re-introduction. It's also warranted underlying that those nutritional patterns represent a difficult challenge to face for someone who at regular times and may be not suitable for those diagnosed with clinical conditions that necessitate introduction of food frequently because of metabolic changes induced by assuming their drugs (e.g. diabetes).

Furthermore, it is also interesting to underline some beneficial effects in hormonal and metabolic outcomes. To be more specific, fasting interventions (IF, Ramadan fasting and OF) brings relevant improvements in fasting insulin and insulin sensitivity.[31] Benefits of this diet is possible due to a potential hyperplasia of B cells of pancreatic islets triggered by this dietary pattern.

The magnitude and clinical importance of improvements of body measures and cardio-metabolic outcomes suggest and imply considerations on potential utilize of fasting regimens in the non-pharmacological treatment of several chronic diseases (e.g. diabetes, cancers, cardiovascular diseases) and life-style problems (e.g. obesity, overweight, etc.). Thus, our study support the idea of a promising efficacy of fasting on postponing the beginning of aging and avoiding diseases, reducing the well-known adverse effects caused by chronic pharmacological treatments.

The positive effect of the fasting regimens has also been documented in inflammatory status. The reduced amount of food consumption results in a decrease in the serum concentration of inflammatory markers, such as IL-6, homocysteine, and CRP. [9,16] Thus, these findings suggest the potential transferability of this non-genetic modulator into clinical practice, in treatment of patients with dysregulation of inflammatory apparatus.

By contrast, fasting showed its drawbacks; also, not favorable findings and adverse effects are other aspects to consider in this discussion. Ramadan fasting appeared to augment risk of peptic ulcer complications (e.g. perforation, bleeding) acute mesenteric ischemia, hyperemesis

gravidarum and primary small bowel volvulus on patients with diagnosis of peptic ulcers on treatment, as shown by one SR findings [18]. In addition, this alimentary pattern, as a side effect, might also increase risk of ocular infectious diseases. [19]

In addition, well-being, quality of life and social functionality were not assessed and ascertained in any identified SR. Indeed, eligible studies reporting data on those dimensions of health status were not found. The lack of findings on these measures hampered the possibility of definitive conclusions on the influence of fasting regimens on all aspects of health, according to the well- known 1948 definition of health status provided by the World Health Organization (WHO) [32].

Results from this systematic overview are limited by some weakness that must be considered and mentioned. Firstly, most of the included SRs were conducted on specific populations. To be more specific, while observational studies on Ramadan fasting were carried out in Islamic countries, RCTs on IF were mostly brought in America. Therefore, the results are not completely applicable and generalizable to global populations. Secondly, meta-analyses were not performed on all identified outcomes due to the absence of reported data required for statistical and quantitative analysis. As a result, the inclusion of meta-analysis on all the identified variables and outcomes could have potentially conduct to dissimilar assumptions. Third, we did not find studies focusing specifically on cognitive functionality, well-being, quality of life and social functionality. This weakness hampered our ability to suggest and conclude that fasting have promise as a method of improving several important health parameters. Fourth, the Amstar tool showed a good methodological quality of some selected SRs, but many reviews did not appear to follow robust study designs. Indeed, rating of the quality of the studies included was judged low to moderate and, for this reason, our results must be treated with caution because due to bad methodological quality of some RSs. The last limitation that has to be mentioned is the small size of studies reporting data on the impact of fasting in children, the very old people, and underweight individual.

Nevertheless, among the strengths of this work, it is possible to cite a comprehensive search strategy using multiple sources to retrieve studies relevant to our PICO. Furthermore, two authors independently selected and extracted data from the included studies. Thus, this mitigate the effect of potential selection bias.

CONCLUSIONS

Conclusively, in adult populations, fasting regimens showed potential beneficial effects on several health indicators and risk factors (e.g. fasting insulin, insulin sensitivity body weight, lipid profile) for non-communicable chronic diseases. Although some findings are not of relevant clinical interest and despite some adverse effects, fasting interventions result in improvements of some functional outcomes such as inflammatory status and hormonal and metabolic parameters. Nevertheless, some specific health dimensions (cognitive function, well-being, quality of life) were not assessed and ascertained by the included SRs. Thus, in the future, further RCTs or cohort studies with good methodological quality and larger sample sizes are needed in order to better understand fasting health benefits and the underlying biological mechanism.

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TABLES

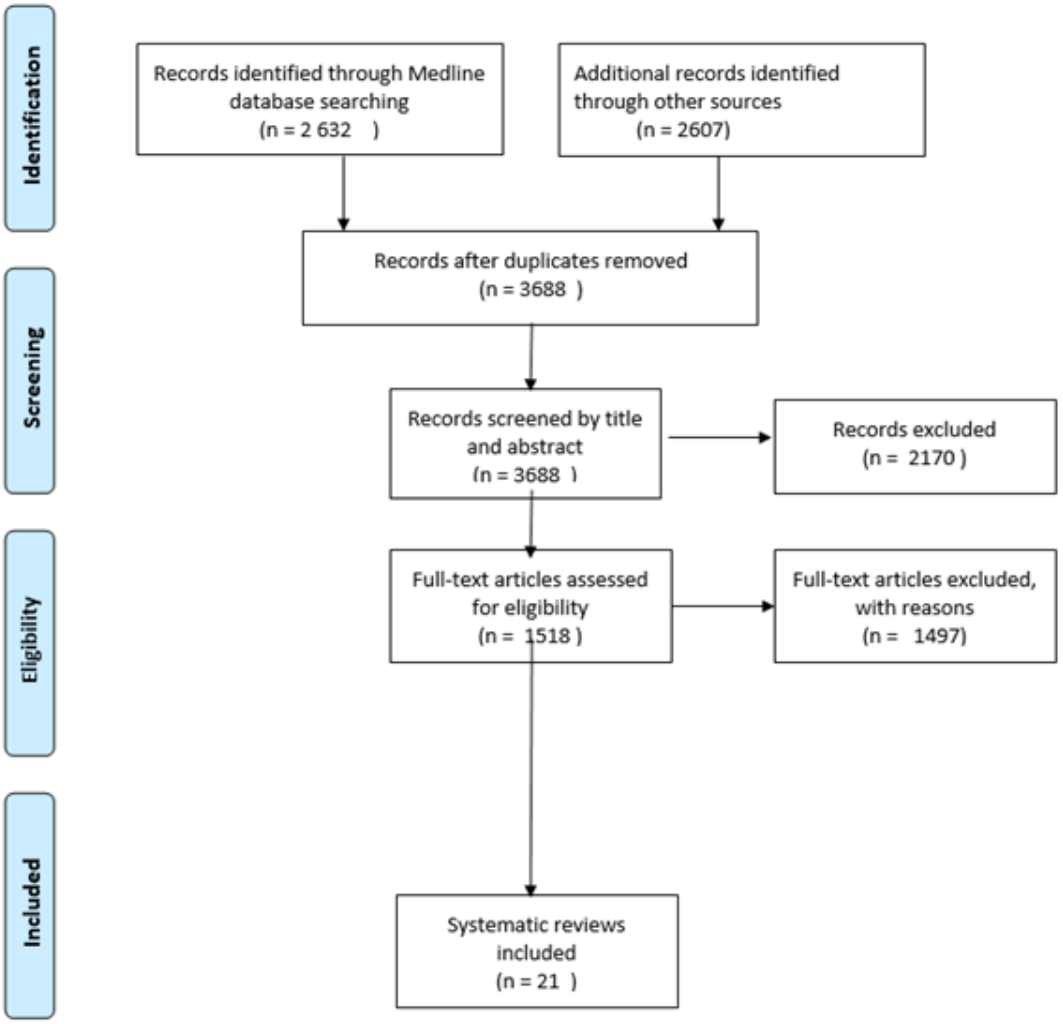
Table 1. — *AMSTAR score (class) for each included systematic reviews (SRs).* AMSTAR is a measurement tool to assess the methodological quality of the included SRs. AMSTAR ranges from 0 (low quality) to 11 (optimal quality).

Author	Year	Fasting Regimen Analyzed	Number of enrolled participants	AMSTAR score (class)	AMSTAR CLASS
Lazarou C. et al.	2010	Orthodox Fasting	724	4,5	2
Sadeghpour S. et al.	2012	Ramadan	10735	4,5	2
Sadeghirad B. et al.	2012	Ramadan	1258	8,5	4
Salim I. et al.	2013	Ramadan	NA	3,5	2
Kul S. et al.	2014	Ramadan	1476	9,5	4
Bragazzi N.L. et al.	2014	Ramadan	2521	3,5	2
Barnosky AR et al.	2014	Intermittent	861	3,5	2
Horne B.D. et al.	2015	Intermittent	796	3,5	2
Seimon R.V. et al.	2015	Intermittent	1765	5,5	2
Bragazzi N.L. et al.	2015	Ramadan	NA	2,5	1
Mazidi M. et al.	2015	Ramadan	NA	4,5	2
Bragazzi N.L. et al.	2015	Ramadan	NA	3,5	2
Turin T.C. et al.	2016	Ramadan	NA	8,5	4

Alhamandan et al.	2016	Intermittent	1193	7,5	3
Lettieri – Barbato D. et al.	2016	Intermittent	NA	8,5	4
Koufakis T. et al.	2017	Orthodox Fasting	2661	5,5	2
Adawi M. et al.	2017	Ramadan	1704	3,5	2
Mo'ez Al-Islam E. Faris et al.	2018	Ramadan	311	7,5	3
Harris L. et al.	2018	Intermittent fasting	400	8,5	4
Fernando H.A. et al.	2019	Ramadan	2947	9,5	4
Glazier J.D. et al.	2019	Ramadan	31374	10,5	4

TITLES OF FIGURES

Figure 1. — *PRISMA flow diagram adapted for a systematic overview.* The following flow chart summarizes and describes the selection process of SRs, from the identification of records to the final inclusion phase.



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P. Anil babu