CUBE guidelines for hematology:

harmonization and implementation issues.

Marchetti Monia, Billio Atto, Liberato Nicola Lucio, Barbui Tiziano,

Barosi Giovanni, Quaglini Silvana, Pane Fabrizio

on behalf of the Italian Society of Haematology.

ABSTRACT

Background

Clinical practice guidelines (CPG) are evidence-based tools supporting everyday clinical practice. Therefore, several institutions and scientific societies regularly produce CPGs, however major inconsistencies can be found among basic recommendations, which limit their validity and applicability. Harmonization among CPGs has been standardized by ADAPTE, but it still remains a huge effort. Ontologies are formal descriptions of concepts populating a knowledge domain. CPG representations through an ontology-based format permit a greater insight into inconsistencies and ambiguities and allows an interactive electronic implementation, which can enhance usability of and adherence to CPGs.

Aims

To describe the guideline harmonization and implementation project started in the year 2014 by the Italian Society of Hematology.

Methods

The ADAPTE toolkit suggests strategies for searching, appraising and comparing CPGs. AGREE is the standard tool used for appraising CPG quality. GRADE methodology is used to develop new evidence-based recommendations for clinical questions formulated according to the PICOT (population, intervention, comparator, outcome, time) format. GUIDE is a knowledge managing system allowing formalization, combination and adaptation of medical and organization processes. The NG Editor allows to draw the CPG content in an algorithmic format and to settle a specific vocabulary.

Results

The Italian Society of Hematology settled a hematology-specific CPG harmonization process including a specific list of sources for CPG retrieval. CPGs are systematically compared and the knowledge domain implicitly reported by CPG is also formalized through and ontology-based editor. Some inconsistent recommendations can be harmonized thanks to explicit representation of underlying concepts though an ontology-based editing. Other inconsistent recommendations are designated for a GRADE-based

reformulation. Six different formats, such as 6 faces of a CUBE, are to be implemented for the CPGs: interactive web pathway, interactive “app”, hypertext, Adobe Acrobat extended text, pocket text, pocket text in Italian language.

A pilot phase was completed: frontline therapy for patients with mantle cell lymphoma was addressed. Five retrieved CPGs reported a few partially consistent and several inconsistent recommendations. Ontology-based CPG editing allowed adaptation steps and suggested solutions for solving inconsistencies.

Conclusions

Evidence-based medicine is facing the era of harmonization and implementation. Standard evidence-based tools do not straightforward solve such major hurdles but can support innovative processes for CPG production and dissemination. Ontology-based CPG representations are useful aids for harmonization and electronic fruition. Multiple-faceted CPGs are expected to be better integrated into clinical practice and enhance adherence.

INTRODUCTION

Clinical practice guidelines (CPGs) are pragmatic tools, usually consisting of a list of narrative recommendations based on the best available evidence, developed to assist health care providers in decision-making. Methods for translating evidence into recommendations have improved and the overall quality of CPGs is progressively ameliorating. The rapid proliferation of local, national and international CPGs, however, disclosed two major shortages, namely frequent inconsistencies among CPGs and poor adherence to CPGs.

Two major causes of inconsistencies have been hypothesized, namely differences in the appraisal and interpretation criteria of the same body of evidence and differences in the translation process of evidence into recommendations. In order to overcome this limitations, harmonization projects (ADAPTE, C-CHANGE) have recently been started for guiding rational endorsement, adaptation or reformulation of externally elaborated guidelines [ADPTE, ref C-CHANGE]. Unfortunately, adaptation versus “de novo development” of CPGs did not reduce time or resource commitments [Harrison 2013]. Moreover, established tools for the assessment of CPG quality do not allow a structured and comprehensive assessment of the content (i.e. reliability and validity) of CPG recommendations [Eikermann 2014].

Factors affecting physicians’ adherence to CPG has long been studied: paper-based format and length of CPGs were reckoned to be relevant hurdles, since they prevent integration of CPGs into the work-flow. Nevertheless, in order to make a CPG computable, i.e. a locally integrated algorithm providing information that can be used quickly at the point of care, decision points and ontologies of the CPG need to be made explicit. Successful implementation of locally-adapted CPG in the workflow was reported by large excellence institutions such as the Kaiser Permanente [Davino-Ramaya]. Finally, adherence to CPG was also greatly affected by lack of a regular updating process.

The Italian Society of Haematology (SIE) started a CPG development process in 1994: the SIGN grading was used up to 2009 and GRADE system afterwards; all CPG were published in a paper format: overall 18 CPGs were published and 2 updated. In May 2014 SIE started a comprehensive guideline project with a twofold aim of disseminating regularly updated, high-quality, interactive CPG that can enter the everyday work-flow of Italian hematologists. In order to respect the project feasibility, SIE endorsed the ADAPTE process for harmonization of consistent recommendations from existing guidelines, but preferred to adopt a hybrid (adaptation plus de novo) guideline development strategy, taking advantage of an ontology-based description of the CPG content [GUIDE] that facilitated retrieval of inconsistencies and implementation into an algorithmic format. The multifaceted product of this process was designated “CUBE” guideline.

Herein we present the methodology issues that were peculiarly outlined in this project along with a pilot phase regarding mantle-cell lymphoma (MCL) management.

METHODS

1-GUIDELINE DEVELOPMENT

The “classical” life cycle of a CPG [SIGN handbook] includes organization steps, selection of topics, literature search, elaboration of recommendations, peer review, dissemination, implementation, audit and review. However, the CUBE project innovated twofold the CPG life-cycle: literature search and elaboration of recommendation were generally replaced by CPG retrieval and harmonization; dissemination and implementation included both narrative and computational formats.

2-GUIDELINE HARMONIZATION

A plethora of CPGs is overrunning hematology, while only a few excellence institutions regularly develops local pathways, therefore a highly heterogeneous adoption of national, local and international CPG is observed. Developing original national CPG could not override the ascendance of international, regularly updated and easily disseminated CPGs. However, harmonization of existing good-quality CPG has the potential to set a unique national standard, to ameliorate the quality of the product and to allow adaptation to national peculiarities, such as epidemiology, regulatory issues, habits and expertise.

The ADAPTE Process provides a systematic approach to adapt guidelines produced in one setting for use in a different cultural and organization context. It includes four phases: 1) problem formulation; 2) CPG retrieval and appraisal; 3) CPG selection and comparison; 4) harmonization of recommendation by adoption or adaptation, according to the applicability to the local context. Adopted and adapted recommendation need to receive grading according to GRADE, irrespectively of the grading system used by the originator CPGs.

3-GUIDELINE REPRESENTATION

The content of a CPG can be profitably be synthesized through authoring tools, also called “Guideline Ontologies”. In general, an ontology is a formal conceptualization of a domain: it allows to list the taxonomy of the domain concepts (named “objects”) along with their relationships. In the context of CPGs, Ontologies are well-defined formalisms that provide models for every action (task) that could be suggested in a guideline, such as choosing a therapy, administering a therapy, gathering information , planning to monitor, giving advice to patients. Each task can have a goal, a trigger (pre-conditions) and post-conditions, as well as temporal constraints. Moreover, an ontology uses a standard terminology in order to avoid ambiguities. The most used standard terminologies are provided by the Unified Medical Language System, a resource of the US National Library of Medicine.

Several tools can support editing CPG in an object-based format: EORCT and ESC used PROforma, while AHA stroke guidelines were represented and integrated into clinical charts using GUIDE (http://www.hcklab.org/guide-project.html).

4-GUIDELINE DE NOVO PRODUCTION

GRADE is the standard methodology for developing evidence-based recommendation. It requires that clinical questions are formulated in a PICOT format, that specifies the addressed patient subpopulation, target interventions and their comparator, the critical outcomes relevant for the decision and the time frame. Literature retrieval is PICOT-specific and evidence quality is appraised with specific rules including not only the single study design but the overall quality of the body of evidence. Tables of evidence list the quality and the pooled content of evidence retrieved for each critical outcome. Recommendations in favor or against the intervention, rather that its comparator, are graded strong or weak, according to the risk-benefit balance and to the body of evidence.

5-DISSEMINATION

Textual reports (Adobe Acrobat) of guidelines were the preferred format for CPG dissemination. Texts usually include recommendations, flowcharts, table-format of staging and scores, references, narrative comments on the links between evidence and recommendations. However, textual format allows for ambiguities related to complex semantics and lacks flexibility, since it cannot incorporate context-based specificities. The Web is currently the principal education and evidence source for the practice hematologist, but medical applications for smartphones, i.e. “medical apps”, increase availability of medical textbooks, guidelines and calculators and are progressively being used especially by medical students and young

doctors. Electronic formats allow a timely incorporation of updates, with no time lag, however, many apps do not keep with national peculiarities, such as drug approval for use.

RESULTS

1-ORGANIZATION

The SIE Task Force devoted to Guidelines includes a Strategic Committee, a Methodology Committee and a set of 11 Working Groups, each one assigned to a specific area (Figure 1). Moreover, 11 External Groups provide each Working Group feedback and validation of guidelines.

The Strategic Committee selects members of both the Methodology Committee and of the Working Groups, along with its chairs. The Strategic Committee is also in charge of managing Relationships with Industries and other Entities declared by the members of the Task Force itself.

The Methodology Committee performs retrival and critical appraisal of CPGs and high-quality most recent evidence, describes the content of selected CPG in both a tabular and an algorithmic format, proposes harmonization actions, i.e. adoption or adaptation, and highlights inconsistencies. Finally, the Methodology Committee proceeds to literature revision and produces GRADE tables (evidence tables and informed judgment tables) for addressing inconsistent or orphan PICOTs. Yearly, the methodology Committee performs a literature scan in order to check whether recommendations might need updating.

Working Groups rank the domains according to their priority for the hematology community, through a transparent consensus process. Domains are formulated in a Patient-Intervention format. Working Groups also anticipate possible orphan or inconsistent of update-needing PICOTS. Working Groups validate the harmonized skeleton proposed by the Methodology Group and selects inconsistent and orphan topics to be addressed. At the end of the process, Working Groups guide external validation of the CPG, list legal and economic aspects of the CPG, and help editing and implementation.

2-HARMONIZATION

Retrieval is conducted in the listed web sites and databases (Table 1) through specific keywords, according to the Patient-Intervention addressed. We chose CPG as identified by three criteria, all of which need to be fulfilled: 1) list of prescriptive recommendations for health-care workers; 2) association of recommendations with scored quality of evidence and/or strength of the recommendation; 3) endorsement by an institution/scientific society/agency. Selection criteria for CPG include English language and latest updating date from 2010 or after. Selected CPG are appraised with the AGREE tool by two independent reviewers: inconsistent score are discussed face-to-face. Finally, the recommendations of selected CPGs are reported in a synopsis table (matrix) indexed with one PICOT per row and one CPG per column. The guidelines achieving highest AGREE scores will be used a referral backbone: clinical questions will be formerly extracted from it, possibly in a PICOT format, and subsequently compared with other CPGs.

In a pilot phase we retrieved and appraised the CPGs related to a Population-Intervention dyad: mantle cell lymphoma (MCL) – first-line therapy. We retrieved 5 guidelines: only two of them were developed according to GRADE. AGREE score ranged from 25% to 57%, the weakest areas being applicability, editorial independence and stakeholders.

Major inconsistencies among guidelines regarded the criteria used to choose a therapy plan. Analysis of ontologies allowed us to classify the decisional criteria used for prompting frontline choices into 7 classes: age, performance status, comorbidity, biologic aggressiveness (blastoid variant, proliferation index), clinical presentation (indolent disease, symptoms, nodal disease), prognostic score (MIPI, IPI), tumor burden (included stage). Each guideline incorporated only a small subset of the above decisional criteria and overlap among guidelines was minimal. The decision to defer treatment, which is reserved only to selected patients, was recommended to be based on the presence of “indolent disease” by 4 out of 5 CPGs, however, no standard definition of “indolent” disease is available. Lymphoma-related symptoms were also advocated by 2 CPGs as a criterion for starting therapy, but the decision to treat was overall poorly structured: implicit

judgement was to consider deferred treatment for patients with none of the listed criteria prompting treatment.

Age and limited stage were the decisional criteria suggested by 4 CPGs for choosing an appropriate frontline therapy. A number of possible frontline chemo-immunotherapies was listed for advanced-stage patients not eligible to transplant: major recommendations were to choose Rituximab-bendamustine and/or Rituximab-CHOP, however, an explicit ranking of the available therapies was reported by only 2 guidelines. Rituximab maintenance was recommended only by most recently updated CPGs and was not limited to patients treated with rituximab-CHOP.

3-REPRESENTATION

We chose to represent retrieved CPGs with NG-editor, a JAVA-based editor developed by the University of Pavia for the GUIDE project. The GUIDE project is a knowledge managing system allowing formalization, combination and adaptation of medical, organizational and health care information and processes. The editor allows to build imbricated algorithms and to build a specific library of terms. A free licence for use was granted to the Methodology Committee.

The Methodology Committee first represents with GUIDE the highest scored CPG, i.e. that appraised with the highest AGREE score, and subsequently integrated the flow with missing objects reported by other selected CPG. The resulting algorithm shows a map of common and missing or inconsistent objects and/or relations as in Figure 2.

We edited harmonized information from the 5 above guidelines with a GUIDE format (Figure 3). In the Web and app version of the algorithm, each box is a hyperlink to calculators, tables and texts including the supporting guideline recommendations, evidence and references.

4-INNOVATION

Inconsistent PICOTS are investigated and possible reasons for inconsistencies are listed by the Methodology Committee. Orphan PICOTS are matched with highest quality evidence produced in the last two years. Relevant inconsistent or orphan PICOTS are then faced by the GRADE methodology and evidence tables are produced.

The comprehensive algorithm and set of recommendation needs approval by the Working Group. The Working Group assign adopted and adapted recommendations a GRADE-based grading of the strength of the recommendation, irrespectively of the grading system used by the original CPGs.

We found inconsistent recommendations to rituximab-bendamustine rather than rituximab-CHOP for frontline treatment of advanced-stage MCL patients not eligible to high-dose therapy. Therefore, a PICOT was formulated including severe adverse events and progression-free survival as critical outcomes and a time frame of 3 years.

5-IMPLEMENTATION

CUBE guidelines are implemented in 6 versions: the main language used is English. The principal dissemination route is the Web, however a “mobile” version of the guideline is also developed. Both these electronic “faces” disassemble the guideline into pathway information, evidence information, definition and classification information. The classic textual version, on converse, includes all the pieces of information in a “pocket” and an “extended” version: the “pocket” version can be downloaded in an Italian and an English Adobe Acrobat version, while the “extended” version is available both as hypertext and as Adobe Acrobat document. Printable formats of checklists, scores, diagnostic and response criteria are allowed to be downloaded separately.

Electronic versions of the guidelines are based on the algorithmic format of the CPG, which is fully interactive: narrative and informative texts and links are accessible through the algorithm boxes. Calculators are integrated into the electronic CPG.

Updates are regularly highlighted in the Web and mobile (“app”) versions.

DISCUSSION

CPG have been progressively assigned a number of missions: knowledge summaries, clinical pathways, legal support, evidence-based support for reimbursement decisions, education tools, standards of care, practice checklists for everyday health-care, legal references, tools for quality control and improvement, basics for technology assessment and cost containment. Thousands of CPGs were produced but a scarce attention has been paid to harmonization and reusing of their knowledge content. Also the legal value of CPGs is questioned when different guidelines are available and no formal adoption process has been implemented locally. Recently the Guideline International Network has formalized a path to adaptation and adoption of CPG through the ADAPTE process. This effort is expected to enhance some issues of CPG quality underpinned by the Institute of Medicine, that are validity and reliability, and consequently accountability, as well as clinical applicability. No prior CPG harmonization project has been attempted in hematology.

Properly disseminated and trusted CPG have produced huge amelioration in the clinical practice: EORTC and ASH/ASCO guidelines for managing chemotherapy-related anemia led to appropriate prescription of erythropoiesis-stimulating agents in 68% of anemic cancer patients versus a 17% proportion before guideline dissemination (Ludwig 2009). A web-based clinical guidance system based on EORTC guidelines showed to enhance clinical effectiveness of anemia treatments (van Erps 2010). Smartphone applications for health-care workers are still being regulated, however, the present project needed to be up-to-date with future technology.

REFERENCES

- ADAPTE - http://www.g-i-n.net/document-store/working-groups-documents/adaptation/adapte-resource-toolkit-guideline-adaptation-2-0.pdf

- C-CHANGE: Tobe SW, Stone JA, Brouwers M, et al. Harmonization of guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE Initiative. CMAJ. 2011 Oct 18;183(15):E1135-50.

- Harrison MB, Graham ID, van den Hoek J, Dogherty EJ, Carley ME, Angus V. Guideline adaptation and implementation planning: a prospective observational study. Implement Sci. 2013 May 8;8:49. doi: 10.1186/1748-5908-8-49.

- Eikermann M, Holzmann N, Siering U, Rüther A. Tools for assessing the content of guidelines are needed to enable their effective use – a systematic comparison. BMC Research Notes 2014, 7:853

- Davino-Ramaya C[1], Krause LK, Robbins CW, Harris JS, Koster M, Chan W, Tom GI. Transparency matters: Kaiser Permanente's National Guideline Program methodological processes. Perm J. 2012 Winter;16(1):55-62.

- Rozati H, Shah SP, Shah N. Smartphone applications for the clinical oncologist in UK practice. J Cancer Education 2014; 30(2):367-73

- Ludwig H, Aapro M, Bokemeyer C et al (2009) Treatment patterns and outcomes in the management of cancer-related anemia in Europe: findings from the Anemia Cancer Treatment (A.C.T.) study. Eur J Cancer.
- Joanna Van Erps & Matti Aapro & Karen MacDonald & Pierre Soubeyran & Matthew Turner & Hans Warrinnier & Tara Albrecht & Ivo Abraham. Promoting evidence-based management of anemia in cancer patients: concurrent and discriminant validity of RESPOND, a web-based clinical guidance system based on the EORTC guidelines for supportive care in cancer. Support Care Cancer (2010) 18:847–858.
- Martínez-Pérez B, de la Torre-Díez I, López-Coronado M, Sainz-de-Abajo B, Robles M, García-Gómez JM. Mobile clinical decision support systems and applications: a literature and commercial review. J Med Syst. 2014 Jan;38(1):4

- Van Erps J, Aapro M, MacDonald K, Soubeyran P, Turner M, Warrinnier H, Albrecht T, Abraham I. Promoting evidence-based management of anemia in cancer patients: concurrent and discriminant validity of RESPOND, a web-based clinical guidance system based on the EORTC guidelines for supportive care in cancer. Support Care Cancer. 2010 Jul;18(7):847-58.

- SIGN 50: A guideline developers' handbook website http://www.sign.ac.uk/guidelines/fulltext/50/index.html

TABLE 1. Sources for CPG retrieval.

WEB SITE	ORGANIZATION
www.g-i-n.net	Guideline International Network
www.guidelines.gov	National Guidelines Clearinghouse
www.library.nhs.uk/guidelinesfinder/	
www.icsi.org/knowledge/	Institute for Clinical Systems Improvement (ICSI)
www.uptodate.org	UPTODATE
www.cancercare.on.ca	Cancer Care Ontario Practice Guideline Initiative
www.nzgg.org.nz/	New Zealand Guidelines Group
www.nhmrc.gov.au/	National Health and Research Council (Australia)
www.cma.ca/En/Pages/clinical-practice-guidelines.aspx	Canadian Medical Association CPG Database
www.gacguidelines.ca	Guidelines Advisory Commitee
www.sign.ac.uk/guidelines/index.html	Scottish Intercollegiate Guidelines Network (SIGN)
www.nice.org.uk/page.aspx?o=ourguidance	National Institute for Clinical Evidence (NICE)
http://www.e-cancer.fr/soins/recommandations/cancers-hematologiques	Istitut National du cancer
http://www.bmlweb.org/consensus_lien.html#Hématologie	Bibliothèque mèdicale AF Lemanissier
www.siematologia.it	SIE
www.bcshguidelines.com	BCSH
www.leukemia-net.org	ELN
www.sisetonline.org	SISET
www.dgho.de www.onkopedia-guidelines.info	DGHO DGHO & OeGHO
www.hematology.org	ASH
www.nccn.org	National Comprehensive Cancer Network
www.asco.org	ASCO (US)
www.esmo.org	ESMO
www.aieop.org	AIEOP
www.ehaweb.org/eha-partners/collaborations/national-societies/listing-of-national-societies/	EHA list of European Societies
www.cochrane.org/reviews	The Cochrane Library
www.crd.york.ac.uk/crdweb http://www.york.ac.uk/inst/crd/crddatabases.htm#HTA	Centre for Reviews and Dissemination Health Technology Assessment Database
www.campbellcollaboration.org	The Campbell Library
www.eppi.ioe.ac.uk/cms/	Evidence for Policy and Practice Information and Co-ordinating Centres
health-evidence.ca	McMaster Universuity – Health Evidence
www.fda.gov/cder/guidance/index.htm	Food and Drug Administration
www.ema.europa.eu	EMA

FIGURE 1. Organigram of the SIE Guideline Task Force.

FIGURE 2. CUBE guidelines development process.

The process starts in the upper left corner: the Working group (WG) elaborates a patient-intervention script (i.e. Unfit elderly patient with untreated symptomatic CLL – First line treatment). The further steps are retrieving of clinical practice guidelines (CPG), their selection and critical appraisal. The backbone content of a selected CPG is than reported graphically, as an algorithm of ontologies, and textually, as a set of clinical questions (PICOTS) accompanied by recommendations. Inconsistencies of other CPGs with the backbone CPG are then assessed. As a final result, a list of "adopted & adapted" recommendations is produced in both textual and graphic format. A list of PICOTS orphan of specific recommendations and of PICOTS with inconsistent recommendations by different CPG is also produced: such PICOTS are addressed by GRADE methodology in order to produce novel recommendations. At this point the process requires validation by the Working Group and the External Panel as to produce the final CPG. By following the arrows one can flow through the final steps of the process in the bottom line to dissemination phase which includes narrative and graphical Web and mobile applications.

WG stays for Working Group

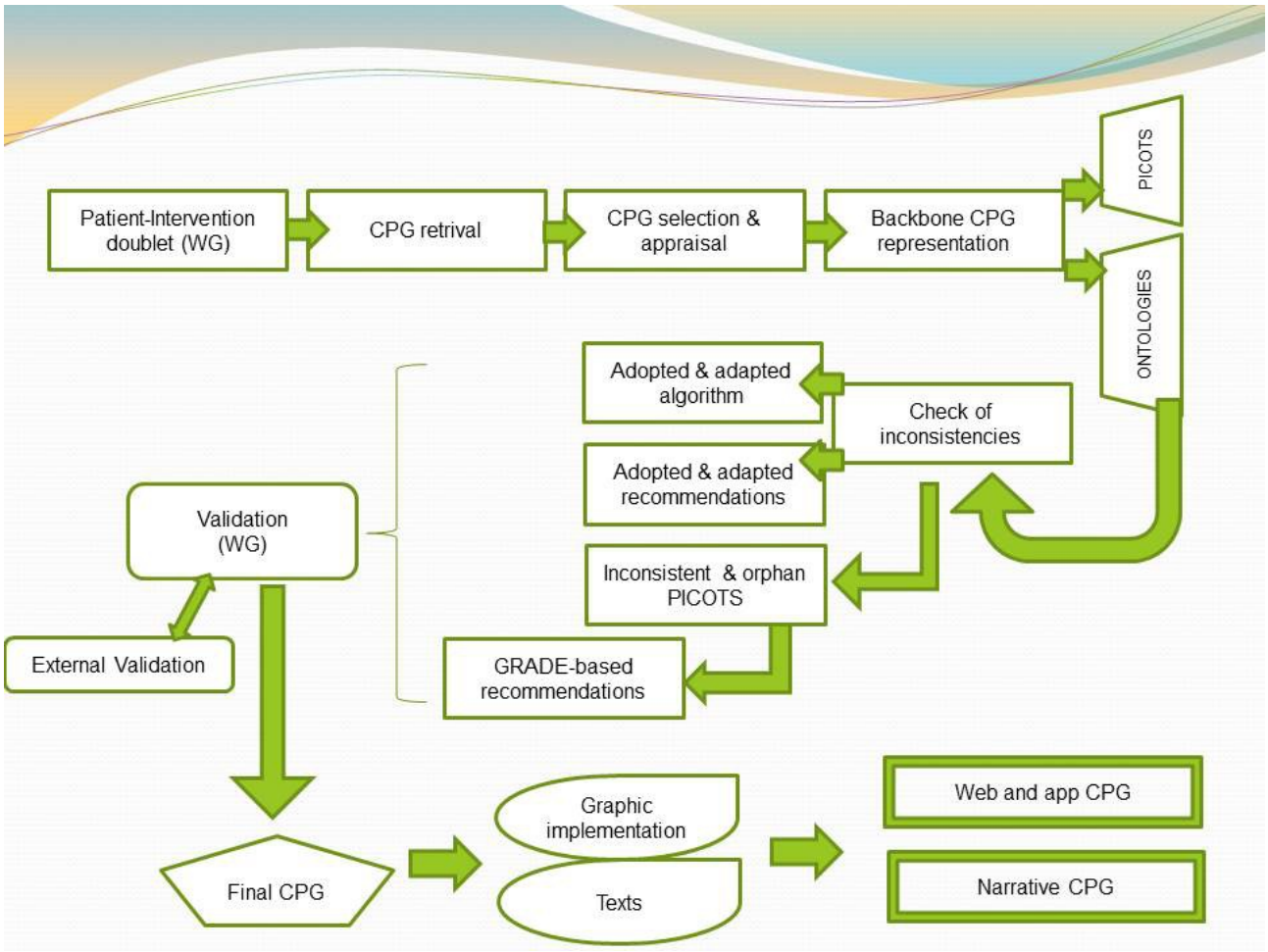
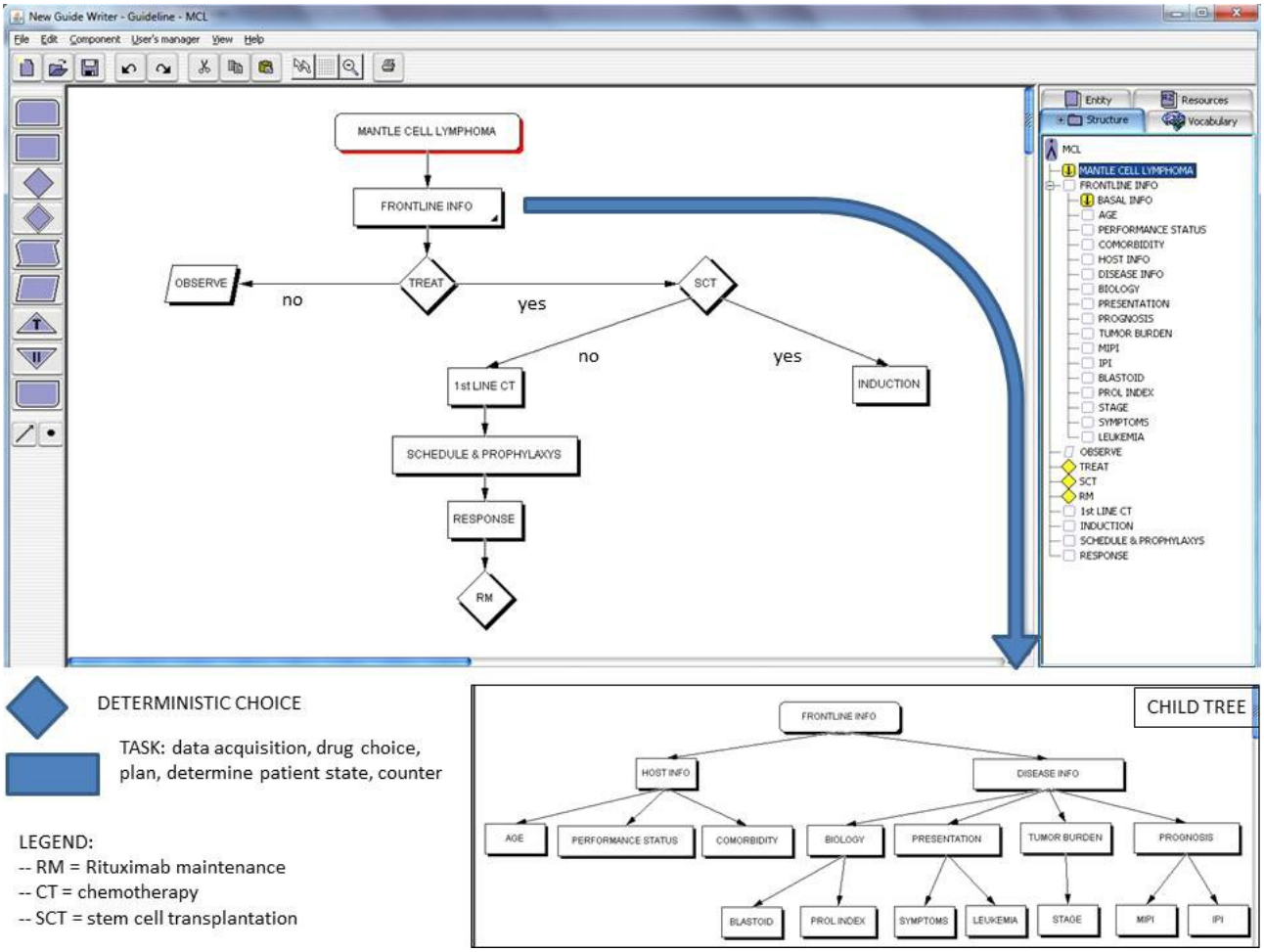


FIGURE 3. GUIDE format for MCL guidelines.

Logical and temporal flow of basic clinical actions are represented: complex actions are decomposed. Decomposed actions are represented with child trees. A sample child tree illustrates the set of information to be gained in order to settle the decision whether to start therapy: the pieces of information are categorized as ontologies and classified according to ontology hierarchy.



DETERMINISTIC CHOICE

TASK: data acquisition, drug choice, plan, determine patient state, counter

LEGEND:
-- RM = Rituximab maintenance
-- CT = chemotherapy
-- SCT = stem cell transplantation