RB-D3.4

Method of representation of BP guideline through Standardised notations/ languages for graphical representation of healthcare processes

Platform for sharing best practices for management of rare diseases

(*RARE-Bestpractices*)

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Introduction

Bridging the gap between clinical research and everyday healthcare practice requires finding ways to support guideline developers (health professionals, methodologists, epidemiologists, statisticians, and others) in making guidelines more understandable and implementable by users (clinicians, patients, and others). This awareness is the base on which National Research Council of Italy has developed its task by searching and implementing standardized languages / notations for the graphical representation of a guideline (TASK 3.4 - *Represent the processes defined in a BP guideline on a specific RD Standardised*). In this paper, we report the approach we used. The first step was to perform a literature analysis for searching which standards languages / notations are applied in literature to graphically represent health care processes (see chapter 1). We were looking for standardized notations or languages (reported in chapter 2) to use in the representation of a guideline (in chapter 3 a case study is reported). The last step was to evaluate the readability and comprehensibility of the graphical representation by submitting to the project partners a questionnaire (results are presented in chapter 4).

All the described activities were done also thanks to the collaboration of other partners: Servicio Canario de la Salud / Fundación Canaria de Investigación Sanitaria, Healthcare Improvement Scotland).

1. Literature analysis for defining the standards methods for the graphical representation of guidelines

1.1 Background

The importance of working toward quality improvement in healthcare implies an increasing interest in analysing, understanding and optimising healthcare processes.(1) These processes may involve a network of heterogeneous components, each one being an agent with freedom to act and with adapting capabilities, and may be influenced by the emerging of self-organized behaviours. Such a complex nature may produce unpredictable overall results.(2-4) Healthcare processes can be classified, into two macro categories: Patient care processes, and organizational or administrative processes.(5) Patient care processes are executed according to a diagnostic–therapeutic cycle, comprising observation, reasoning and action, directly linked to the patient. Organizational/administrative processes are patterns that support medical treatment via the co-ordination of different people and organizational units. Here we focus on patient care process within Clinical Practice Guidelines (CPGs) and on their site-specific adaptations referred to as Clinical Pathways.(6) CPGs have emerged as a source of support for health professionals, policymakers, and patients/public aspiring to make healthcare decisions on the basis of the best available evidence.(7) CPGs, as defined by World Health Organization (WHO) and Institute of Medicine (IoM),(8,9) aim to improve quality of care, reduce unjustified practice variations and reduce healthcare costs.(10) However, issues exist that can prevent optimum implementation of CPGs. When analysing the characteristics of the CPG, the “complexity of the guideline” is the most frequently described factor influencing its implementation.(11) Guideline developers tend to focus on specific tasks rather than on time-extended processes such as care plans.(12) When guideline recommendations are unclear, users may question their rigor and reliability. It is therefore essential that interpretability is addressed within the guideline development phase.(7) Schünemann et al.(13) reported that bridging the gap between clinical research and everyday healthcare practice requires finding ways to help guideline developers (health professionals, methodologists, epidemiologists, statisticians, and others) in making guidelines understandable and implementable by users (clinicians, patients, and others). These two characteristics, declined in terms of clarity of presentation, applicability, and use and evaluation, are key factors (hence focus of specific sections) in internationally recognised methodological documents for CPG development and appraisal.(14-18) Faster learning, higher retention, and better compliance can be obtained by the use of clinical algorithms that graphically display decision logic, sequences and timing of activities, especially when dealing with complex or unclear situations.(19) The adoption of graphic algorithms is also recommended for improving guideline use.(20)

The aim of the present work, as part of a more general effort on the development of methods for clinical practices guidelines applied in the challenging area of Rare Diseases,(21, 22) is to identify standardised (i.e. approved as ISO standard by the International Organization for Standardization) languages and notations for graphical modelling and representation adopted for patient care processes and potentially usable during the development of clinical guidelines or pathways.

1.2 Methods

We have done an analysis of the international literature searching in the following databases: Global Health, Ovid Healthstar, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®. The strategy combined the following terms: healthcare process, process of care, patient care process, patient care management, and visual / graphic / representation / notation / language / description / model / diagram / workflow. Only articles since 2000 were considered. To complete the search, the reference lists of relevant studies were screened and experts consulted to identify further studies satisfying the selection criteria. Web of Science (WoS) and the Google Scholar were also searched to identify potentially relevant additional papers citing the selected studies.

The eligibility criteria we have used are: studies describing or assessing standardised languages and notations for graphic representation of any healthcare process, including applications in the development, representation, communication, dissemination or implementation of clinical practice guidelines or pathways were considered for inclusion. Only full text of original studies published in English, Italian or Spanish were included. No restrictions were imposed regarding study design, and health condition. Papers concerning mathematical and stochastic models were excluded. Applications outwith the healthcare setting or applied to purely organizational issues were also excluded.

Five reviewers were involved in the selection process and the disagreements regarding eligibility were resolved by consensus: Carlo Giacomo Leo, Pierpaolo Mincarone, Giuseppe Ponzini, Saverio Sabina (National Research Council of Italy), Maria M. Trujillo-Martín **(**Servicio Canario de la Salud / Fundación Canaria de Investigación Sanitaria). Jan Manson (Healthcare Improvement Scotland) helped in the searching phase.

1.3 Results

The retrieved articles reported experiences of graphical modelling standardised languages / notations suitable for the medical domain. Adopted languages / notations are reported in Table 1.

Table 1: Standardised graphical modelling languages / notations adopted in the medical domain

Modelling language/notations	**Working Team involved as reported in the articles**	**Items covered in the representation**
Business Process Model and Notation (BPMN)	*Process knowledge holders*: health professionals, resident and doctoral students, and administrative staff. *Process analysts*: Software engineers, consultant-moderator as IT project director	Sub-processes, tasks, gateways (decisions/evaluations), sequence flows, parallel branches, events, actors, data objects, message flows
Unified Modeling Language ® - UML ® (activity diagram)	*Process knowledge holders*: physicians. *Process analysts*: medical informaticians; Experts in operational research / management, science applied to health care, and systems modelling and simulation; experts in Computer science.	- Tasks, gateways (decisions/evaluations), sequence flows, parallel branches, roles, bottlenecks (as notes), messages
Petri net	*Process knowledge holders*: physicians. *Process analysts:* engineers; experts in Computer science	Tasks, gateways (decisions/evaluations), sequence flows, parallel branches, roles.

2. Description of the different methods for the representation of guidelines

2.1 UML

The Unified Modeling Language ® - UML® (23) is a graphical language that offers a standard way for visualizing, specifying, constructing, and documenting a system's blueprint, including business process logic and system functions as well as programming language statements, database schemas, and reusable software components.(24) UML® has several diagrams which can be grouped into three categories representing static application structure, general types of behaviour, and different aspects of interaction.(25) The objective of UML® is to provide system architects, software engineers, and software developers with tools for analysis, design, and implementation of software-based systems as well as for modelling business and similar processes.(26) Also in this case, the capacity of UML© to model business processes and ICT systems can be exploited in order to support the execution of the modelled processes.

2.2 BPMN

Business Process Model and Notation - BPMN(27) is a standard notation and consists of one diagram, called the Business Process Diagram, which is based on a flowcharting technique tailored for creating graphical models of business process operations (networks of graphical objects, which are activities and the flow controls that define their order of performance). The primary goal of the BPMN is to provide a notation that is readily understandable by all process users, from the analysts that create the initial drafts of the process logic to the process people who manage and monitor those processes.(28) BPMN allows modelling on several levels of details from macro to micro process representations. BPMN is also supported by graphical object properties that enable the generation of the Business Process Execution Language, a standard executable language for specifying actions within business processes with web services.(29)

2.3 Petri net

Petri nets are oriented graph representing processes and are made up of two types of nodes, places (circles) and transitions (squares), connected by directed arcs.(30)

Arcs cannot link nodes of the same type. Transitions may fire when 'tokens' (resources) are present in the corresponding input place(s). When a transition is fired, tokens are consumed from its input place(s) and produced for its output place(s). Token distribution in a certain time represents the state of the system. Classical Petri nets allow modelling states, events, conditions, synchronisation, parallelism, choice and iteration. To efficiently describe real processes, these features are not sufficient, thus many extensions to classical Petri nets have been proposed. The so-called 'high level' Petri nets allows the addition of colours, hierarchy and time to the basic representation.(31,32)

3. Representation of a NICE guideline - Myeloma: diagnosis and management

3.1 Why we choose the Nice Guideline

As reported in the Grant Agreement Annex I - *Description of Work*, the graphical representation of the processes defined in a Best Practice guideline would have been done either on one of the pilot guidelines developed under the Task 3.3 or on an already published guideline selected among the ones collected in the *RAREGUIDELINE* Database (Task 4.2). As discussed during the General Assembly meeting #4 (28-29 April 2016 - Santa Cruz de Tenerife, Spain), the two pilot guidelines (*Catastrophic Antiphospholipid Antibody Syndrome* and *Sickle Cell Disease*) address specific issues and do not deal with the full healthcare process. This aspect, specifically linked to the piloting activity under the Task 3.3, was judged as determining a limited showcase of the potential advantages of the graphical representation of a clinical practice guideline. Consequently, it was agreed to focus the efforts of the Task 3.4 on other broad-in-scope guidelines. *Healthcare Improvement Scotland* (HIS) offered to support in the selection of a guideline from the ones included in *RAREGUIDELINE* Database.

Two guidelines were identified and proposed by HIS:

- Multiple myeloma: diagnosis and management (https://www.nice.org.uk/guidance/ng35); *it is published by NICE in England;*
- Evidence-based management of sickle cell disease (http://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf); *this is an American guideline.*

After an analysis of the two documents, we found no big difference for the aim of our activity and decided to work on the NICE guideline on Multiple myeloma.

Myeloma is a malignancy of the plasma cells that normally produce immunoglobulin. It affects multiple organs and systems, including the bones, kidneys, blood and immune systems. Myeloma management is complex and challenging. Effective treatments have been developed over the past 15 years, and although myeloma is still incurable, these treatments have led to improvements in overall survival and quality of life. However, myeloma treatment increasingly involves expensive drugs and frequent hospital visits. Complications of myeloma and myeloma treatment cause an increasing long-term strain on supportive and palliative care services, and on carers. The NICE guideline covers areas in which there is uncertainty or variation in practice and deals with adults (aged 16 years and over).

3.2 Specificity of the selected piece of guideline

The specific aim of the proposed exercise (i.e., to verify whether a graphical representation of a clinical practice guideline with a standardized language / notation can help readers to correctly understand the reported recommendations) led us to represent not the whole guideline but a couple

of specific topics that, based on our judgment, could have given the exact idea of the added value that a graphical representation can provide to the understanding of healthcare processes. In this way, it was possible to focus the attention on some paradigmatic aspects that we discussed with RARE-Bestpractices partners during the General Assembly meeting #5 (23 November 2016, Rome).

After an overall analysis of the entire document, we decided to focus on the *Laboratory investigations* and *Imaging investigations* (the referred text is reported as Annex 1 to this document).

Laboratory investigations and *Imaging investigations* are both part of the diagnosis phase whose formalization is of great interest for physicians that, when dealing with a rare disease, may not be accustomed to recognize and, subsequently, manage the pathology.

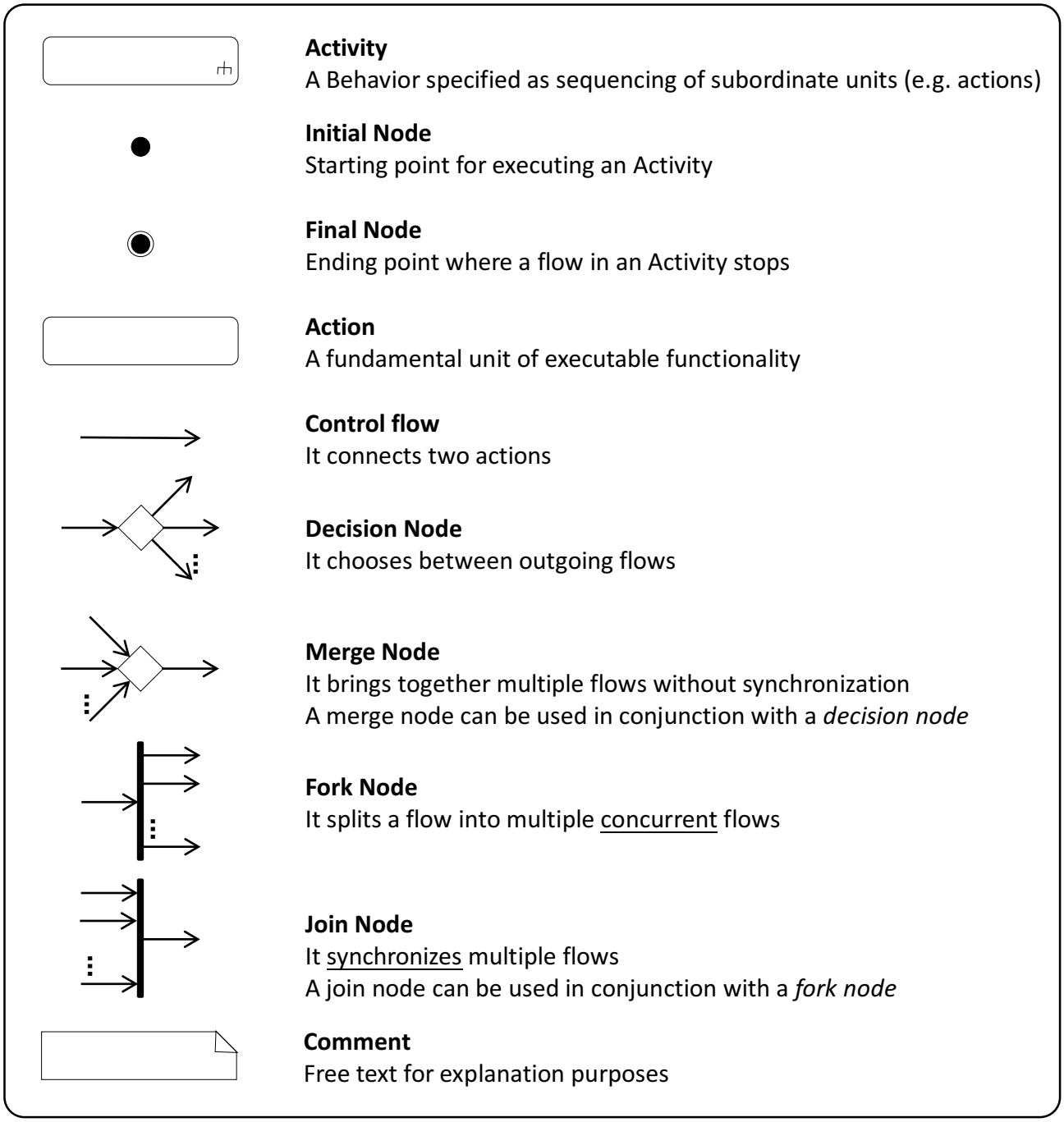
3.3 Graphical representation

Among the three standardised languages / notations of which there is evidence of suitability for the medical domain (see section 2), we decided to adopt UML ® 2.5 as implementation-independent language. In fact it is an international standard issued by a well-established group with a strong foundation in the industry (OMG), it has already gone through a maturing process and it has been widely adopted. While UML ® 2.5 shares these characteristics with BPMN 2.0, we think the former can be more simple to understand for non-technicians. In fact, we are concerned with the early stages of CPG model development, in particular with the modelling of procedural knowledge fragments in the CPG text, and we firmly believe that, in this case, comprehensibility should prevail.

After the identification of the procedural fragments in the CPG text (see 4.2), a first modelling of these fragments was carried out independently by three researchers (Carlo Giacomo Leo, Pierpaolo Mincarone and Saverio Sabina). Activities were considered at the same level of granularity as the CPG text describes explicitly. Represented processes were reviewed for consensus by the same three researchers.

The following figure reports the adopted symbols - adapted from Object Management Group, 2015.(26)

Figure 1 – UML ® 2.5 – Adopted symbols



Besides the procedural aspects, an important issue to be considered when representing a guideline is the strength of the recommendations. NICE Guidelines reflect the strength of the recommendation with clear indications on their wording.(33) NICE refers to 3 levels of certainty: recommendations for activities or interventions that *should* (or *should not*) be used; recommendations for activities or interventions that *could* be used; recommendations for activities or interventions that *must* (or *must not*) be used.

We directly recalled the NICE methodology and reported [should], [could], [must] as an accompanying notation in the name of the represented activities.

The realised diagrams are reported in the following figures.

Figure 2 – Graphical Representation of the *Laboratory investigations*

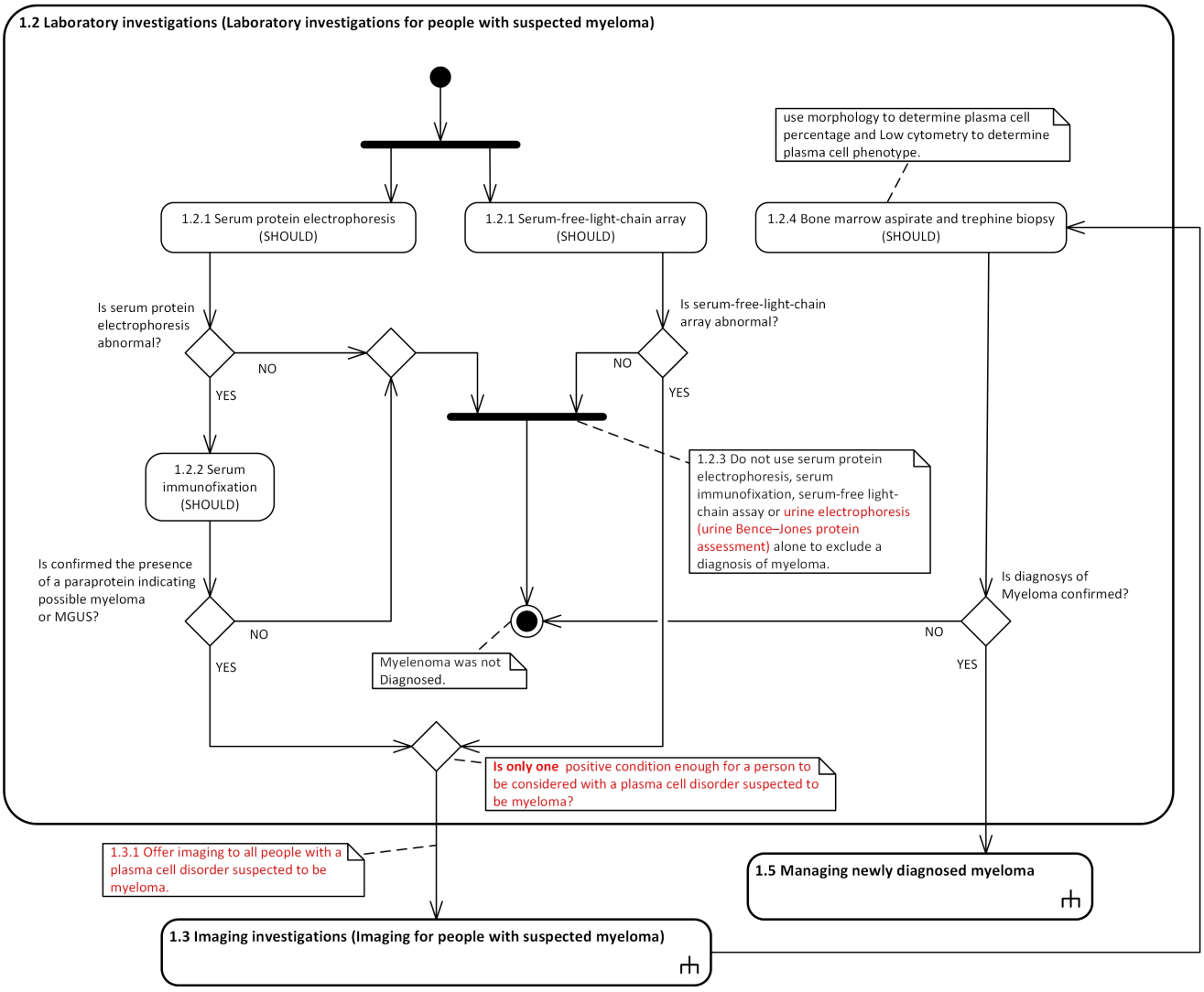
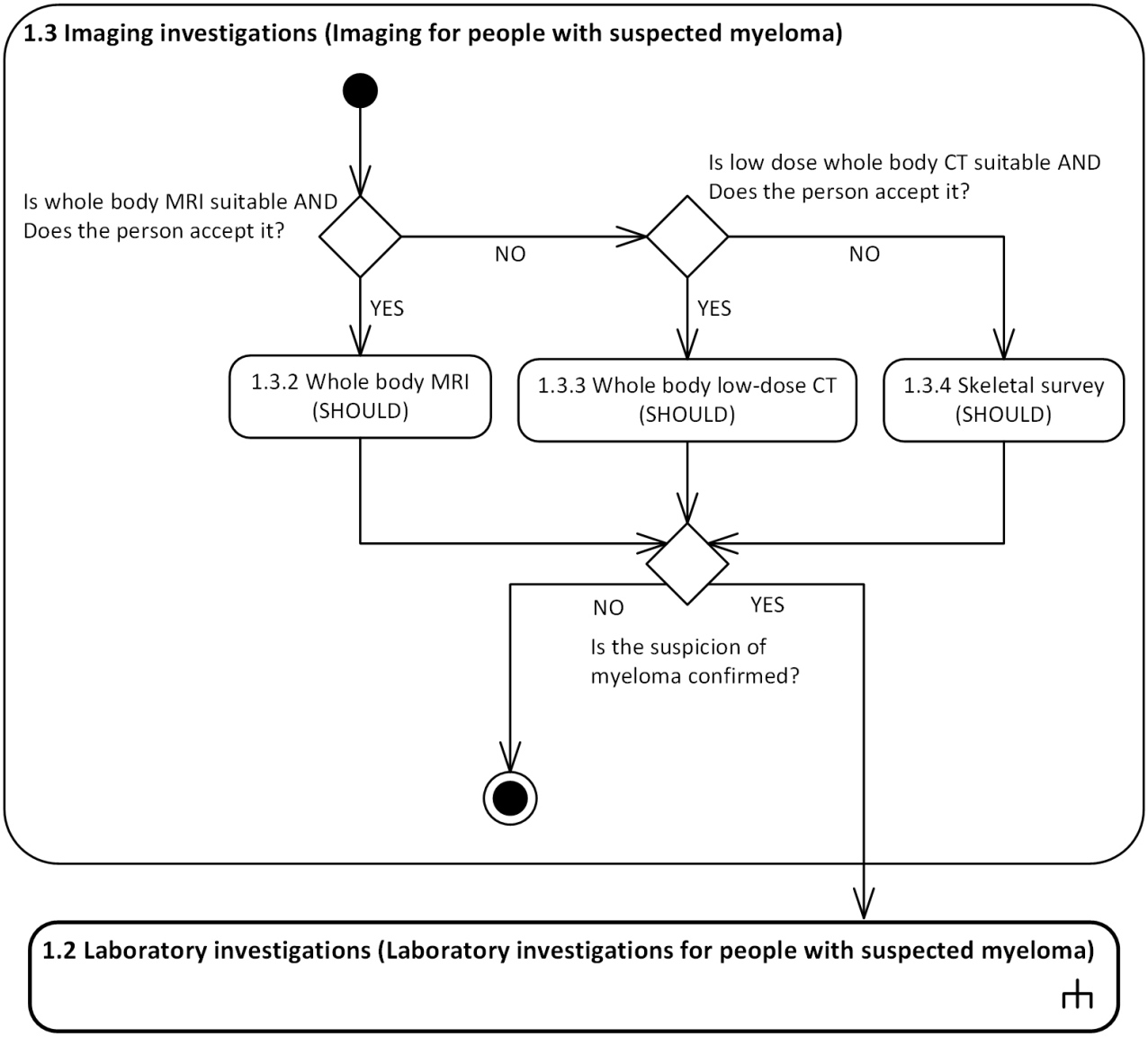


Figure 3 – Graphical Representation of the *Imaging investigations*



While we have not encountered any particular problem in representing recommendations 1.3 (Figure 3), there are some issues that, in our opinion, are not clearly reported in the text of the recommendations 1.2 and that require both a deep knowledge of the disease and the full reading of the guideline. Critical aspects have been represented with red text in Figure 2.

1) Urine electrophoresis (urine *Bence–Jones* protein assessment) is only mentioned in the recommendation 1.2.3 where it is said that, as the other reported techniques (protein electrophoresis, serum immunofixation, serum-free light-chain assay), it should not be used alone to exclude a diagnosis of myeloma. The text does not clarify in which condition this exam should be done and in which relation it is with the other tests for determining a plasma cell disorder suspected to be myeloma.

2) While recommendation 1.2.3 specifies that none of the four tests should be used alone to exclude a diagnosis of myeloma, it is not clear if 1, 2 or 3 (if also considering the urine electrophoresis) positive tests are enough to determine a plasma cell disorder suspected to be myeloma. In Figure 2, we reported the case that one positive exam is enough. On the contrary, the *Merge Node* before activity 1.3 should have been substituted by a *Join Node*.

3) The Control flow that ends in the Activity 1.3 is not textually described in the section 1.2 *Laboratory investigations* but in the section 1.3 *Imaging investigations*. This is a typical example of the need to jump among different sections of the guideline that could potentially cause the loss of information (on the process to follow) for users not accustomed with the disease (as it can be for a rare disease). A graphical representation could be of great help in overcoming this limitation.

We are confident that, if the graphical representation had been done during the guideline definition, the first and second critical issues (urine and number of positive results for determining a plasma cell disorder suspected to be a Myeloma) would have suggested the panel the opportunity of re-wording the recommendations.

3.4 Evaluation of the representation

The graphical representations were evaluated in terms of readability, comprehensibility, relation with the corresponding textual description. For this purpose, a questionnaire has been generated (see Annex 2) which was filled in by project partners during the General Assembly meeting #5 (23 November 2016, Rome).

The questionnaire contains both closed questions and open questions. The three closed questions regard the readability (Q #1) and the comprehensibility (Q #2) of the graphical representation, as well as a forced preference among the graphical and the textual representation of guidelines (Q #3). If the answer is “uncertain” or “no”, open comments are required (Q #1b, Q #2b, Q #3b). The forth question is completely open and stimulates additional comments about the graphical representation: usefulness and quality of the representation, interpretability and presence of ambiguity, etc. (Q #4).

As described in the previous paragraphs, the specific aim of the proposed exercise and related questionnaire is to test whether a graphical representation of a clinical practice guideline with a standardized language/notation can help readers to correctly understand the reported recommendations.

Results of answers to the closed Questions (Q #1, Q #2, Q #3) are reported in the paragraph “ANALYSIS OF THE CLOSED ANSWERS”. Although added open comments are related to Q #1 – Q #3 questions, these are separately analysed, together with Q #4, in the paragraph *QUALITATIVE* “ANALYSIS OF THE OPEN ANSWERS”.

ANALYSIS OF THE CLOSED ANSWERS

Results of answers to the closed Questions (Q #1, Q #2, Q #3) are synthetized in Table 1.

Concerning Question 1, most of respondents (11 out of 12) answers “yes”, positively confirming that the graphical representation is easily readable with respect to the diagram structure and layout. Only 1 respondent answers “uncertain”. Only 3 out of 12 respondents add comments (Q #1b), and those notes are stimulating, as described in the following paragraph.

Regarding Question 2, most of respondents (8 out of 12) answers “yes”, positively confirming that the graphical representation is easily comprehensible with respect to the diagram content and the represented processes. Four respondents answer “uncertain”. Seven out of 12 add interesting comments and suggestions (Q #2b), as described in the following paragraph.

With reference to Question 3, there is not a confirmation that the proposed visualization is better than textual description. In fact, only half respondents (6 out of 12) answers “yes”, while 2 answer “uncertain” and 4 answer “no”. Moreover, most of them (9 out of 12) adds interesting comments on how the two modalities of representation are complementary (Q #3b), as described in the following paragraph.

Table 1: Answers to Closed Questions

Closed Questions	Yes	Uncertain	No
Q #2 - *Concerning the diagram structure and layout, is the graphical representation easily readable?*	11	1	0
Q #2 - *Concerning the diagram content and the represented processes, is the graphical representation easily comprehensible?*	8	4	0
Q #3 - *Is the proposed visualization better than textual description?*	6	2	4

QUALITATIVE ANALYSIS OF THE OPEN ANSWERS

Concerning the open answers to Question 1b, the subject answering “Uncertain” reports a difficulty: “it does not reflect how this would work in practice”. Two other respondents add suggestions on how to ameliorate the visualisation: e.g., use larger fonts at key inflection points; use different colours for the different graphical elements (See Table 2).

Regarding the open answers to Question 2b, although most of respondents to Question 2 has confirmed that the graphical representation is easily comprehensible with respect to the diagram content and the represented processes, three of the ones who answered “yes” add comments. The seven comments comprise: (a) suggestions on how to ameliorate the graphical representation; (b) some difficulties in their interpretation of the visualisation (See Table 2).

Table 2: Suggestions and difficulties related to the graphical representation

	Suggestions on how to ameliorate the graphical representation	Difficulties in the use or interpretation of the visualisation
Q #1b	- Use larger fonts at key inflection points; different colours also welcome. But you need to use sparingly and in order to attract attention (S7) - Please consider putting the different graphical elements in different colours (S8)	- It does not reflect how this would work in practice (S4)
Q #2b	- This needs to be qualified in the legend -> what it means & alternatives (S1) - Please see the diagram for comments (included) (S3) - It may need more information with numbers and references. (S4) - Please make initial node clearer, e.g. by adding a title of what the starting point is (S7) - In the example showed there are gaps and lines should not be crossed between them (S10)	- Yes, after reading explanations (S2) - It seems a little more complicated than daily practice is (S5)

S: Subject (or Respondent)

With reference to the open answers to Question 3b, the trend does not confirm that the proposed visualization is better than textual description. Instead, the trend underlines the opinion that both the graphical representation and the textual description are useful for the comprehension of guidelines. The two modalities of representing guidelines are generally perceived as complementary (6 respondents out of 12) and many respondents envision the necessity to maintain both the modalities, as both have strengths and weaknesses. Some respondents suggest that visualisation is useful since it can help identify gap in guidelines where more ambiguity is present. Some other respondents believe that visualisation has the minus that it does not carry the full meaning and context of the textual description (See Table 3).

The Question 3 was intended just to verify what relationship there might be between graphical representation and textual description. The related results are encouraging because they tell us that both the ways of representing guidelines are valuable and their usage was perceived correctly by respondents. In this perception, none of the two modalities is considered as unneeded, being the end-user the one who decides “if” and “when” consulting which one of them.

Concerning the open answers to Question 4, most of respondents directly or indirectly confirms that graphical representation is clear and useful if accompanied by the textual description. They further underline that visualisation helps identify gaps, quickly directs to relevant part of guidelines, clearly shows means (See Table 3).

Table 3: Matrix on the *Plus* and *Minus* of the Graphical representation and Textual description

	Graphical representation	Textual description
Plus	Q3b - It can help identify gap in guidelines where more ambiguity is required. Q3b - This is a potential useful tool for guideline development for some topics but perhaps not all. Q4 - It is clear and useful. Q4 - It helps identify gaps. Q4 - It directs quickly to relevant part of guidelines. Q4 - Clearly shows means.	Q3b - It carries the full meaning and context of guidelines. Q3b - Some people might prefer text. *Q3b - It is useful for guideline development for all the topics.*
Minus	Q3b - It should be accompanied by a textual description. Q1b - Uncertain: Because it does not reflect how this would work in practice. Q2b - Uncertain: It seems a little more complicated than daily practice is.	*Q4 - It is less direct.* *Q4 - It does not help identify gaps.* *Q4 - It does not help identify ambiguities.*

In *Italic*, we indicated the thoughts - regarding the textual description - that are not directly expressed by the respondents, but are indirectly deducible by other complementary phrases regarding the graphical representation. The necessity to highlight those thoughts descends from the fact that most of the questions – with the exception of Question #4 - focus on the graphical representation, while the comparison with the textual description remains often implicit. The matrix makes this implicit comparison clearer and more visible.

4. Conclusions

The present deliverable is the result of the Task 3.4 – *Represent the processes defined in a BP guideline on a specific RD*. Standardized languages/notations for the graphical modelling of healthcare processes have been identified: UML®, BPMN and PetriNet. Current evidence does not demonstrate any advantage of one over the others in healthcare applications. Nevertheless, it is our opinion that UML® is the simpler to be understood by non-technicians involved in clinical practice guideline developers / readers.

The piloting phase, focused on the NICE guideline *Multiple myeloma: diagnosis and management*, allowed to highlight several points of possible misunderstanding in the textual representation. These results, discussed during the Project General Assembly meeting #5, show that both the graphical representation and the textual description are useful for the comprehension of guidelines. The two modalities of representing guidelines are generally perceived as complementary and have strengths and weaknesses. Based on the results of our work, we can state that the use of a graphical representation can bridge the gap between clinical research and everyday healthcare practice, supporting guideline developers (health professionals, methodologists, epidemiologists, statisticians, and others) in making guidelines more understandable and implementable by users (clinicians, patients, and others).

5. Bibliography

1. Edwards N. Can quality improvement be used to change the wider healthcare system? Qual Saf Health Care. 2005;14(2):75.

2. Lipsitz LA. Understanding health care as a complex system: the foundation for unintended consequences. Jama. 2012 Jul 18;308(3):243-4.

3. Wilson T, Holt T. Complexity science - Complexity and clinical care. British Medical Journal. 2001 Sep;323(7314):685-8.

4. Luke DA, Stamatakis KA. Systems Science Methods in Public Health: Dynamics, Networks, and Agents. In: Fielding JE, editor. Annual Review of Public Health, Vol 33. Palo Alto: Annual Reviews; 2012. p. 357

5. Lenz R, Reichert M. IT support for healthcare processes - premises, challenges, perspectives. Data & Knowledge Engineering. 2007 Apr;61(1):39-58.

6. Rotter T, Kinsman L, James E, et al. Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs. The Cochrane database of systematic reviews. 2010(3):Cd006632.

7. Treweek S, Oxman AD, Alderson P, et al. Developing and evaluating communication strategies to support informed decisions and practice based on evidence (DECIDE): protocol and preliminary results. Implementation Science. 2013 Jan;8:12.

8. Institute of Medicine. Clinical practice guidelines we can trust. Washington (DC): National Academies Press (US); 2011.

9. World Health Organization. Estonian Handbook for Guidelines Development; 2011.

10. Peleg M. Computer-interpretable clinical guidelines: A methodological review. Journal of Biomedical Informatics. 2013 Aug;46(4):744-63.

11. Francke AL, Smit MC, de Veer AJ, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: A systematic meta-review. BMC Medical Informatics and Decision Making. 2008 2008-09-12;8(1):38.

12. Fox J, Black E, Chronakis I, et al. From guidelines to careflows: modelling and supporting complex clinical processes. Studies in health technology and informatics. 2008 2008;139:44-62.

13. Schunemann HJ, Woodhead M, Anzueto A, et al. A vision statement on guideline development for respiratory disease: the example of COPD. Lancet. 2009 Feb-Mar;373(9665):774-9.

14. GIN-McMaster. GIN-McMaster Guideline Development Checklist. 2014 [cited 17/09/2015]; Available from: http://cebgrade.mcmaster.ca/guidelinechecklistonline.html

15. Schunemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. Cmaj. 2014 Feb 18;186(3):E123-42.

16. World Health Organization. WHO handbook for guideline development – 2nd ed; 2014.

17. Agree Next Steps Consortium. Appraisal of Guidelines for research & evaluation II; 2013 September 2013.

18. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting, and evaluation in health care. Preventive medicine. 2010 Nov;51(5):421-4.

19. Rosenfeld RM, Shiffman RN, Robertson P. Clinical Practice Guideline Development Manual, Third Edition: A Quality-Driven Approach for Translating Evidence into Action. Otolaryngology-Head and Neck Surgery. 2013 Jan;148:S1-S55.

20. Gagliardi AR, Brouwers MC, Palda VA, Lemieux-Charles L, Grimshaw JM. How can we improve guideline use? A conceptual framework of implementability. Implementation Science. 2011 2011-03-22;6(1):26.

21. Sejersen T, Del Giovane C, Filippini G, et al. Methodology for production of best practice guidelines for rare diseases. Rare Diseases and Orphan Drugs. 2014;1(1):10-9.

22. Taruscio D, Morciano C, Laricchiuta P, Mincarone P, Rare-Bestpractices Consortium. RARE-Bestpractices: a platform for sharing best practices for the management of rare diseases. Rare Diseases and Orphan Drugs. 2014;1(1):5-9.

23. Unified Modeling Language (UML). Available from: http://www.uml.org/

24. Object Management Group. Unified Modeling Language Specification. 2000.

25. Object Management Group. Introduction to OMG's Unified Modeling Language (UML). 2005. Available from: http://www.omg.org/gettingstarted/what_is_uml.htm

26. Object Management Group. OMG Unified Modeling Language ® (OMG UML ®) Version 2.5. March 2015. Available at http://www.omg.org/spec/UML/2.5/.

27. BPMN Specification - Business Process Model and Notation. Available from: http://www.bpmn.org/

28. White SA. Introduction to BPMN. 2004.

29. White SA. Using BPMN to Model a BPEL Process. 2005.

30. Murata T. Petri nets: properties, analysis and applications. Proc IEEE 1989;77(4):541–79.

31. Genrich HJ, Lautenbach K. System modelling with high level Petri net. Theor Comp Sci 1981;13:109 – 36.

32. Jensen K. Coloured Petri nets. Basic concepts, analysis methods and practical use. In: EATCS Monographs on Theoretical Computer Science. Berlin: Springer–Verlag, 1992.

33. NICE. Developing NICE guidelines: the manual (PMG20). Chapter 9 *Developing and wording recommendations and writing the guideline*. April 2016. Available at

https://www.nice.org.uk/process/pmg20/chapter/9-developing-and-wording-recommendations-and-writing-the-guideline.

6. Document History

Date	Author	Changes
17/11/2016	All the authors	First draft completed (analysis of questionnaire missing)
14/12/2016	All the authors	Analysis of questionnaire (answers collected during the GA meeting #4)
16/12/2016	K. Ritchie (HIS)	Suggested edits for tables; misprint correction in affiliation
21/12/2016	General Assembly	Approval of the Document

Annex 1 – Extract from the NICE guideline *Myeloma: diagnosis and management*

<from the next page on>

NICE National Institute for Health and Care Excellence

NICE guideline

Myeloma: diagnosis and management

NICE guideline

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1.1.4 Refer people who are assessed as needing further psychological support to psychological services.

1.1.5 Advise family members or carers (as appropriate) about the range of available local and national support services at diagnosis, at the beginning and end of each treatment, at disease progression and at transition to end of life care.

1.1.6 For guidance on communication and patient-centred care see the NICE guideline on patient experience in adult NHS services.

1.2 Laboratory investigations

Laboratory investigations for people with suspected myeloma

1.2.1 Use serum protein electrophoresis and serum-free light-chain assay to confirm the presence of a paraprotein indicating possible myeloma or monoclonal gammopathy of undetermined significance (MGUS).

1.2.2 If serum protein electrophoresis is abnormal, use serum immunofixation to confirm the presence of a paraprotein indicating possible myeloma or MGUS.

1.2.3 Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) alone to exclude a diagnosis of myeloma.

1.2.4 When performing a bone marrow aspirate and trephine biopsy to confirm a diagnosis of myeloma, use morphology to determine plasma cell percentage and flow cytometry to determine plasma cell phenotype.

1.2.5 For guidance on the setup of laboratory diagnostic services see the NICE cancer service guidance on improving outcomes in haematological cancers.

Laboratory investigations to provide prognostic information

1.2.6 Use the same sample for all diagnostic and prognostic tests on bone marrow, so people only have to have one bone marrow aspirate and trephine biopsy.

1.2.7 When performing a bone marrow aspirate and trephine biopsy to provide prognostic information:

- Perform fluorescence in-situ hybridisation (FISH) on CD138-selected bone marrow plasma cells to identify the adverse risk abnormalities t(4;14), t(14;16), 1q gain, del(1p) and del(17p)(TP53 deletion). Use these abnormalities alongside International Staging System (ISS) scores to identify people with high-risk myeloma.
- Consider performing FISH on CD138-selected bone marrow plasma cells to identify the adverse risk abnormality t(14;20), and the standard risk abnormalities t(11;14) and hyperdiploidy.
- Consider performing immunophenotyping of bone marrow to identify plasma cell phenotype, and to inform subsequent monitoring.
- Consider performing immunohistochemistry (including Ki-67 staining and p53 expression) on the trephine biopsy to identify plasma cell phenotype and give an indication of cell proliferation, to provide further prognostic information.

1.2.8 Perform serum-free light-chain assay and use serum-free light-chain ratio to assess prognosis.

1.3 Imaging investigations

Imaging for people with suspected myeloma

1.3.1 Offer imaging to all people with a plasma cell disorder suspected to be myeloma.

1.3.2 Consider whole-body MRI as first-line imaging.

1.3.3 Consider whole-body low-dose CT as first-line imaging if whole-body MRI is unsuitable or the person declines it.

1.3.4 Only consider skeletal survey as first-line imaging if whole-body MRI and whole-body low-dose CT are unsuitable or the person declines them.

1.3.5 Do not use isotope bone scans to identify myeloma-related bone disease in people with a plasma cell disorder suspected to be myeloma.

Imaging for people with newly diagnosed myeloma

1.3.6 For people with newly diagnosed myeloma or smouldering myeloma who have not had whole-body imaging with 1 of the following, consider whole-body

Annex 2 – Questionnaire

QUESTIONNAIRE ON GRAPHICAL REPRESENTATION WITH Unified Modeling Language – UML® 2.5

1) Concerning the diagram structure and layout, is the graphical representation easily readable?

YES ☐

UNCERTAIN ☐

NO ☐

1b) If “uncertain” or “no”, can you explain why?

2) Concerning the diagram content and the represented processes, is the graphical representation easily comprehensible?

YES ☐

UNCERTAIN ☐

NO ☐

2b) If “uncertain” or “no”, can you explain why?

3) Is the proposed visualization better than textual description?

YES ☐

UNCERTAIN ☐

NO ☐

3b) If “uncertain” or “no”, can you explain why?

4) Please add any comments on the graphical representation (usefulness and quality of the representation, interpretability and presence of ambiguity, etc.)
