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REVIEW ARTICLE

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Identifying options for oncology therapy regimen codification to improve standardization—combined results of an expert panel and a review

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Abstract

What is known and objective: Chemotherapy drugs are often administered in combinations with predefined interdependent doses and cycle intervals. As yet, there is no global standardization system to describe these complex regimens in a universally comprehensive manner. The aim of this review is to identify which efforts for standardization have been undertaken and which recommendations for databases and nomenclature of chemotherapy regimens are available.

Methods: A literature review was performed to identify all peer-reviewed full-text articles about oncology therapy regimen codification. In addition, the results of this search were evaluated and consensus recommendations from a European expert panel were subsequently added.

Results: This review gives an overview of attempts to standardize chemotherapy nomenclature described in the literature, as well as of previously published identified gaps in regimen codification. In addition, we summarized the suggestions for improvement of chemotherapy codification found in the available literature, combining them with the expertise from a European expert panel of oncology pharmacists.

What is new and conclusions: We believe that one of the most important error-prevention measures is standardization. However, there is a paucity of data how it may be achieved. Currently available data suggest that standardization has a positive impact on usability for data networks, prescription software, safety and the measurement of the quality of cancer care delivery. Standardization is also a strong prerequisite for all discussions including oncology pharmacists and oncologists when evaluating chemotherapy regimen in countries in Europe but also all over the world. The recommendations compiled in this review can help to support overdue standardization efforts in this important therapeutic area.

KEYWORDS
chemotherapy regimen, classification, codification, standard

1 | WHAT IS KNOWN AND OBJECTIVE

The adoption of electronic tools is critical for improving healthcare safety in multiple ways. Their implementation in a national eHealth strategy is essential as it provides the foundation, justification and support for the quality and standardization needed to go forward in a coordinated way. It is also important to strengthen the quality of electronic systems to improve patient safety. This may involve the introduction of electronic health records to replace paper records, having integrated electronic systems that can support clinical decision making or making the tools easier for professionals and patients to use.[1]

For therapy regimens in oncology, this approach has already proven to result in error reductions.[2] Oncology therapy regimens consist of one, or more likely multiple, medications (combination therapy and supportive therapy) with different degrees of complexity and dependencies. Creating a regimen is defining the drugs to be used, their dosage, the frequency and duration of treatments, among other considerations. Such regimens are often identified by acronyms (eg AC= Adriamycin and **C**yclophosphamide or CHOP = (**C**)yclophosphamide, Adriamycin (**H**)ydroxydoxorubicin, Vincristine with the trade name **O**ncovin and **P**rednisolone). However, there is no widely accepted naming convention or authoritative comprehensive standard [3] to which each healthcare institute or each clinical software developer can cross reference their own regimens.[4-6] It takes time, effort and resources to implement electronic tools, and to use and maintain them also requires substantial capacity. It is therefore important to be strategic and to understand the foundations and design of systems in order to ensure the best return on investment and sustainability.[1]

In this review, we present all published efforts in creating standardization of chemotherapy regimen nomenclature as well as electronic approaches in building and using datasets of regimens. In addition, we will summarize all the options for the standardization of nomenclature and codification of chemotherapy identified in the literature and in an expert workshop, as well as the proposed solutions.

2 | MATERIALS AND METHODS

2.1 | Literature review

Published reports were identified, and all abstracts were reviewed for eligibility. For the articles selected, full-text publications were retrieved and reviewed for additional information. Bibliographies from selected key articles and relevant review articles were screened for additional sources.

To identify existing guidelines for oncology therapy regimen codification and published codification strategies, we searched PubMed, Ovid MEDLINE Scopus and Google Scholar for publications in English or German using the terms "database*", "regimen*", "standardi*", "guideline*", "cancer*", "anticancer*", "oncol*", "chemo*", "antineoplast*", "cytotox*", and "codif*". References were excluded if they were therapeutic clinical trials (not "clinical" and "trial*"). Thereafter, we used hand searching in the bibliographies of selected articles to search for additional references. Due to the heterogeneous nature of the literature reflected by the wide variation of search terms that had to be used, the final inclusion of papers was performed based on the relevance for the scope of this article.

2.2 | Suggestions for improvement of codification

Material was discussed during a two days' workshop with five experts from the European Society of Oncology Pharmacy (ESOP) from five different countries (Austria, France, Lebanon, The Netherlands and Spain) in October 2019. During this workshop, a comprehensive evaluation of therapy protocols from various hospitals was also performed to study their degree of comparability and identify gaps in the nomenclature. All gaps identified by this expert panel were compared with those published in the articles from the literature search. During the workshop, the identified disparities were recorded and underwent a root cause analysis to establish the most suitable solutions.

3 | RESULTS

3.1 | Literature review

In total, 13 scientific publications were identified in October 2020 that could be included in the analysis (Figure 1). Of these, four papers referred to one unique ontology system (HemOnc), with a fourth one also stemming from the same research institute. Below follows a description of the identified initiatives, the approaches for standardization in coding or description of regimens that could be extracted are combined in Table 1.

3.1.1 | United States (US) based libraries and codification approaches

The first initiative to perform standardization for the expression and nomenclature of cytotoxic regimens was a joint effort between the National Institute of Health (NIH) and the National Cancer Institute (NCI).[7] These institutes issued a set of guidelines in 1998 which was published online later.[8] It was developed by a group of oncology and clinical pharmacists and submitted to a large panel of pharmacists for consultation and approval. It was not specifically intended for digital application. The guidelines are summarized together with the suggestions from the other scientific papers in Table 1.

The second initiative in the US is the US oncology standardized regimen library. This library is incorporated in the iKnowMed software specifically to enable clinical practitioners to order chemotherapy for individual patients. This library was developed in a multiprofessional

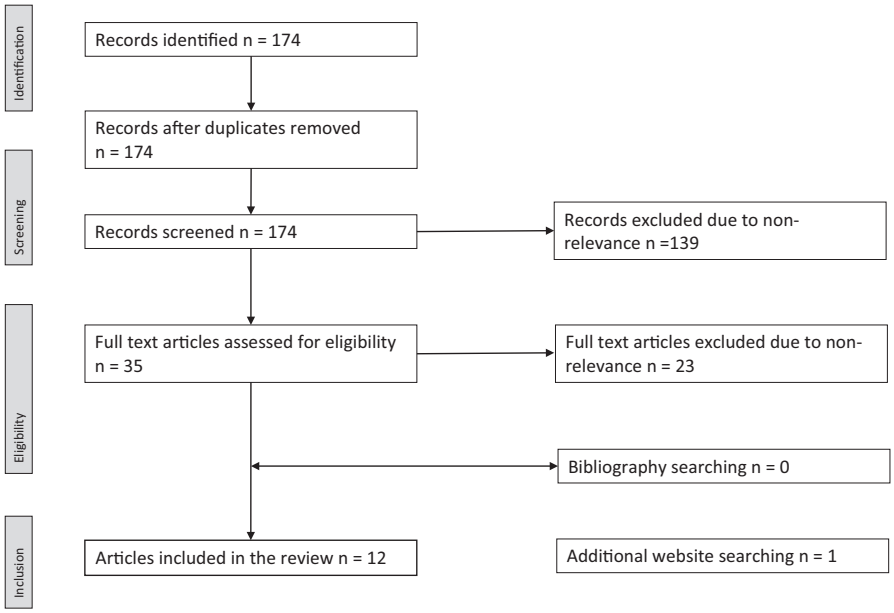

FIGURE 1 Preferred reporting item for systematic reviews and meta-analysis (PRISMA) flow diagram

approach by oncologists, pharmacists and nurses and is used by 900 community-based oncologists in 39 states across the US.[9] During an internal audit, it was found that 75% of regimens in the library required title changes to comply with standardization, 14% required cycle-related changes and 13% required dosing updates. This led to additional standardization for entries into the library.

The third initiative is the HemOnc.org database. This is a non-commercial online freely accessible database started in 2011 through a collaboration of oncologists from several (University) hospitals in the US.[10] As of January 2020, the database comprises >3,000 regimens. A data model, with bindings to multiple external vocabularies such as the National Cancer Institute Thesaurus, was derived from this website later on.[6] A separate publication from this group describes the ontology proposed for cytotoxic regimens, taking into account indication, drug names, schedule and duration. A hierarchic taxonomy was created by use of a specifically developed algorithm that parsed the existing data from the web-based data library.[11] A standard vocabulary was also proposed by this group. A publication stemming from one of the collaborating University groups outlines the development of a machine learning algorithm that uses a data driven method for cancer treatment plan recognition. This application uses pharmacy chemotherapy dispensing orders followed by a sequential mapping method to produce the identified chemotherapy protocols and also includes the sequence of therapy lines. This machine learning approach was accurate in identifying the used regimens in 75% of cases in a sample of 110 patients, when compared to a manually annotated gold standard.[12] In 2020, the HemOnc group published a proposal for a standardized nomenclature for chemotherapy regimens that was also compared to the thesaurus of the US National Cancer Institute.[13]

The fourth and last US initiative, that has been published, was launched in Colorado and consists of an electronic algorithm that can identify specific regimens from source data derived from electronic health records. It was developed specifically for the entities breast cancer, colorectal cancer and lung cancer. It had a sensitivity of 97%–100% for the recognition of first-course systemic therapy with a false-positive rate of 0%.[14]

Overall, these US based initiatives, that are still being developed further, enable the gathering of big data that can potentially be used for real-world safety and effectiveness studies, when they would be coupled with registries with outcome data.

3.1.2 | European based libraries and codification approaches

In Europe, three national initiatives aiming to standardize or codify cytotoxic chemotherapy regimens were found during the literature study, one from the United Kingdom (UK), one from Germany and one from the Czech Republic. The Czech group developed a database in XML named DIOS starting in 2006. They used standardized expressions for the naming of regimens, as well as for the different items forming the core of the regimen (drug names, routes of administration, dosages and intervals). This library contained 260 distinct regimens at the time of publication in 2013.[15] The current status is available in both Czech and English on the Internet.[16]

The German initiative is called Oncopti and consists of a relational database currently comprising over 1400 regimens. It is continuously updated. The data are stored in XML, like in the Czech library, and are available for members of the German Oncologic Society on the Internet.[17] This comprehensive initiative not only adds guidelines for recommended supportive treatment to the core oncology regimens, but also advices on the optimal order of administration of drugs and features the ability to export the library regimens to software systems for ordering and compounding chemotherapy that are widely used in Germany and Austria.[18]

The UK initiative is called SACT and consists of a database containing both adult as well as paediatric oncology treatment regimens. The SACT data are routinely collected from all National Health

TABLE 1 Current options to improve standardizations in regimen codification and nomenclature for chemotherapy treatments in healthcare information systems and published guidelines.

Category & Number	Issue	Suggestion for improvement	References
Drugs			
1	Imaginative names of regimens (eg FEC, TAC) based on abbreviations, INN names are mixed with brand names	Do not abbreviate drug names and use only complete approved generic drug names	[6,7,9,11,13,21], experts
2	Different orders for the same combination (eg FEC/EFC).	Name the protocol in line with the real sequence. Protocols where the sequence of application is essential should be marked as such indicating the reference.	[7,11,13], experts
3	Protocol names that do not indicate the correct sequence of application (either because the acronyms are not in line with the real sequence or because new data have meanwhile shown that another sequence is more effective and/or less toxic)	Name the protocol in line with the real sequence. Protocols where the sequence of application is essential should be marked as such indicating the reference.	[13], experts
4	Drugs that are taken at home by the patient—especially with oral oncology therapies—are frequently ignored in the translation from protocols to hospital medication orders	Include oral therapies in the protocols	[7], experts
5	Liposomal formulations are available with different pharmacokinetic properties, which are critical for their therapeutic effects and adverse effects. In publications and regimen names different conventions are used	Unify the nomenclature of liposomal formulations with consideration of their different properties in the respective regimen (non-pegylated vs. pegylated)	experts
6	Drugs that can be either a co-medication or be part of the cytotoxic regimen (eg dexamethasone as an antiemetic prophylaxis or a premedication to prevent hypersensitivity or as an intrinsic part of the chemotherapy regimen)	Standardize how to indicate whether a drug is used as supportive medication or as a part of the chemotherapy regimen	experts
Dosage & administration			
7	Confusion in abbreviations such as IU, U, USP-U, mg	Write out the abbreviations	[7,11,19]
8	Different names for modes of application (eg bolus versus iv injection—continuous infusion versus x-hour infusion)	Include the route of administration (eg IV, PO,...) and the duration (eg 15 min, 46 h,...) of the infusion together with the shape (eg continuous infusion, short infusion or bolus)	[11,21], experts
9	Differences in expression of the decimal sign, either by a point or a comma (0,5 mg versus 0.5 mg)	Never trail a whole number with a decimal sign followed by a zero (eg use 5 mg instead of 5.0 mg) and always write the dosage with the unit less than the number 1, with a decimal sign preceded by a 0 (eg use 0.125 mg instead of.125 mg)	[7] experts
10	Information about the duration of the infusion is missing, including information about the duration of co-medication such as hydration schedules	Include the route of administration (eg IV, PO,...) and the duration (eg 15 min, 46 h,...) of the infusion together with the shape (eg continuous infusion, short infusion or bolus)	[7,21], experts
Schedules			
11	Protocols starting with day 0 as the first day of the main therapy versus those starting with day 1	Start a protocol always on day 1, premedication may be dated with day −1, −2,.. Day 0 is not used.	[7], experts
12	Different ways how sequences/blocks of therapies are set up (eg, doxorubicin/cyclophosphamide followed by paclitaxel can be spelled AC-T or ACT, or AC-pac or be defined as two independent schedules)	Design how protocols are built (blocks—regimen—protocols)	[9,13,15],experts

(Continues)

TABLE 1 (Continued)

Category & Number	Issue	Suggestion for improvement	References
13	There are protocols where the number of cycles is essential but missing in hospital protocols	Specify the number of cycles when they are fixed	14,19
14	There are protocols where the treatment duration is open (eg until progression or toxicity)	Include the average number of cycles reported in the clinical trial report	14,19
15	Protocols cannot be distinguished from each other because radiation is not integrated analogues to a medication in the regimen.	Integrate radiation therapy in the regimen as a medication (name, dose, route, sequence,...). This makes it possible to recognize that modified doses are due to the combination with radiation and are not a dose modification of a standard protocol	13,19,experts
Miscellaneous			
16	Regional variations or patient specifically adapted regimens	Include source references. If there is no primary literature cited, they may not be considered as defined protocols but could be categorized as "regimen without reference" in case they are used "off label"	6,9,10, experts
17	Protocols, which represent dose reductions, are falsely considered to be independent protocols	Define possible dose ranges according to the related primary literature	10,experts
18	For so-called modified (m) protocols it is not commonly agreed what modification means (FOLFOX / mFOLFOX)	Define and specify the term m (modified)	13,experts
19	Terms like accelerated escalated and intensified are used in a non-standardized way	Define and specify the terms accelerated, escalated and intensified	13,experts
20	The therapeutic intention of the protocol is not available (curative, adjuvant, neo adjuvant, palliative)	Add the therapeutic intention of the regimen	7,experts
21	Information about the study population treated with the protocol described in the reference is missing	Add the characteristics from the study population to make comparisons with the properties of the individual patient who is intended to be treated with the protocol possible Use standardized diagnosing codification like ICD	19

Abbreviations: ICD, International Statistical Classification of Diseases and Related Health Problems, by the World Health Organization; iv, intravenous; po, per oral.

Service (NHS) trusts in the UK and are part of the National Cancer Registration. The SACT stores data not only of the chemotherapy regimen, but also of the patients, diagnoses and outcomes. In addition, the data can be linked to several other datasets from the UK National Cancer Registration.[19]

3.1.3 | Clinical trial protocol standardization approaches

Clinical trial protocols specifically require a clear and consistent method for expressing chemotherapy dosage schedules and treatment regimens, to minimize undue risks to patients. Apart from the Good Clinical Practice Guidelines, the SPIRIT 2013 statement describes the standardized items required to be included in each clinical trial protocol.[20] However, neither GCP nor SPIRIT give exact guidelines on how to define the expression and nomenclature of cancer treatment regimens. For further optimization in the protocolling of clinical trials with oncology drugs, the UK National Cancer Research set up the Chemotherapy and Pharmacy Advisory Service (CPAS) which built a standard template giving specific guidance on all drug-related content in clinical trial protocols. This template aids investigators in providing unequivocal information on treatment regimens through use of a standardized format. In a publication outlining the work of CPAS, data from 176 clinical trial protocols that were reviewed were compiled resulting in a summary of options to leverage standardization concerning drug-related content.[21]

3.2 | Improvement of codification: suggestions from the expert workshop

In a 2-day workshop, held in collaboration with IQVIA as part of the now discontinued Oncology Data Network (ODN) project, gaps in

the nomenclature of regimens derived from different hospitals in 5 different countries were identified and discussed. Examples include the following: (a) the classification of abbreviations (TAC referring in some hospitals to paclitaxel-doxorubicin-cyclophosphamide but in other hospitals to docetaxel-doxorubicin-cyclophosphamide because both brand names of the taxanes start with "T"), (b) the decision on classifying variations of a regimen as one or more distinct regimens (is azacitidine 7 days identical to azacitidine 5 + 2 days in which the weekend is skipped, is continuous radiation identical with radiation 5 days + 2 days break?), (c) if only generic names are used, how will the mapping of liposomal formulations be handled by software applications? and (d) the use of terms like accelerated, intensified and escalated is not clarified and although they are all referring to ways of increasing the dose density of a schedule, the resulting dosages and intervals may differ between protocols from different hospitals, countries or regions. The gaps and opportunities identified were combined with those already described in the literature, and suggestions for standardization were compared and merged with those from the literature (Table 1).

4 | DISCUSSION

We identified twenty-one opportunities for standardization in total that have been described in the literature or were identified by the expert panel with regard to uniform designation and description of regimens used in oncology. This means that as yet, standardization beyond regions or individual countries is still far from implemented. To overcome these issues, a collaborative effort of healthcare professionals as well as their professional bodies, governments and inspection authorities, appears to be warranted. If standardization could be achieved, the use of big data to compare treatments and their outcomes in cancer comes within our reach. The first attempt in this direction on a European level was the ODN project by IQVIA.[22,23] However, this project was halted in 2020. A novel opportunity could come from the European Health Data Space, a project set up by the European Commission, to be executed before 2025.[24]

However, to fill the current gaps that we have detected in this review, several answers to specific issues must be formulated. For example, a directive is necessary to identify the minimum parameters required to describe a regimen, and strategies must be defined how to deal with variants. What is an acceptable variation? For example: can 3-weekly taxane regimens be considered equivalent to low dose weekly administrations of the same cumulative dose? Another issue for future investigations would be to introduce so-called "families of medicines" for therapeutically similar but not identical medicines. This is not required when generics are used as they are considered interchangeable. However, it would be helpful to define them and allowing the use of biosimilars and even clusters like taxanes, anthracyclins and anti EGFR medicines for outcome research. For this purpose, the pharmacological background has to be explored.

In summary, although the publications found by this comprehensive review provide good guidance, and demonstrate the feasibility of standardization on a small scale, there are still remaining issues that have to be solved, before big data sets usable to compare treatments and outcomes on a European or worldwide level can be build.

5 | WHAT IS NEW AND CONCLUSION

To our knowledge, this is the first worldwide approach for a gap analysis of therapy regimens intended to be used in oncology. We believe that one of the most important error-prevention measures is standardization. However, for the description of complex drug regimens used in the treatment of patients with cancer, there is no gold standard yet to reach standardization across regions or countries. The recommendations compiled in this review can help to achieve standardization of oncology therapy regimens that qualifies them for an application to big data sets and automation efforts.

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CONFLICTS OF INTEREST

All authors state no conflict of interest.

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