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Reasoning about bladder cancer treatment outcomes using clinical trials within a knowledge-based clinical evidence approach

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Abstract

Side effects (SEs) and adverse events (AEs) of bladder cancer (BC) treatment have become more prevalent and may impact the effectiveness of the prescribed therapy. Given, the substantial combination of various treatment types and interventions, it is crucial for the urologist and the team of specialists to discern the systematic and local SEs of these treatments for more awareness and vigilance. This was shown within randomized clinical trials (RCTs) which are complex, and their management needs many efforts. RCTs generate a big amount of knowledge that can serve as evidence for future clinical decision making. Current approaches do not discuss semantic integration of different resources. In this paper we propose a knowledge-based BC treatment effects and complication infrastructure (BCTECI) approach to reason and appraise the effectiveness of BC treatments within their related SEs. This optimized treatment outcomes. Referring to ontology features, a knowledge model with semantic queries and logic rules included evidence concluded from the assessed RCTs. Hence, this supports interoperability between RCTs resources and a common treatment ontology. For this, a comprehensive literature search of relevant RCTs was performed systematically in different electronic medical databases. All pertinent RCTs covering BC treatment cases and reporting prescriptions' effectiveness were included in BCTECI knowledge model. This study provided the required taxonomy and semanticization and evaluated the effectiveness of treatment outcomes. Furthermore, it extended the clinical evidence-based knowledge for AEs anticipation with a more efficient treatment prescription and showed whether SEs impact the effectiveness of a prescribed treatment until revocation.

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1. Introduction

Bladder cancer (BC) represents 4% of diagnosed cancers and is ranked as the 7th most frequent cancer site worldwide with an amount of 2.7 million patients [1][2][3]. Each year, around 275,000 people are diagnosed with a bladder tumor with an incidence of 100.1‰ cases men and 20.5‰ cases women [4][5][6]. These tumors are responsible for 2.5% of cancer deaths including treatment adverse events (AEs) deaths [7][8][9].

When diagnosed with BC, the patient is directed to an oncology or urological surgery department. Then, a team of specialists determines the cancer type and staging, then, suggests the most appropriate treatment options [10][11][13]. The team usually includes a radiotherapist, an oncologist, and a urological surgeon [14]. The diagnosed tumor is discussed during a meeting bringing together the various specialists to formulate a treatment proposal [15][16][18]. It is difficult to limit the effects of treatment on cancer cells without affecting or damaging healthy cells. This causes side effects (SEs) which depend mainly on the type of chosen treatment and its extent with relation to the patient's medical history [19][20][21][22][23][24]. On average, around 30% of patients are at high risk of developing short- and long-term SEs which leads to very serious results [25][26][27]. Hence, estimation and effective management of this condition is very important prior the treatment application.

Over the last decade, several studies have investigated the effectiveness, vigilance and responses of treatments applied to patients with BC [28][29][29][30][31]. However, no consistent conclusions about treatments AEs, risks and efficacy have reached among those studies. Adding to that, the significance of various therapy protocols still in controversial. Therefore, a synthesis of current evidence to investigate and predict the possible SEs and efficacy of treatments for BC curation is described in this paper based on randomized clinical trials (RCTs).

There are several challenges with BC research nowadays. Clinicians, oncologists, healthcare providers and patients need to overcome the enormous knowledge and the different factors of hazard within the big amount of data-based information. Clinical trials provide electronic data, which are concentrated on a specific trial, rather than an electronic health record (EHR) or a personal patient-centered track record. Most of which are registered within big various and independent databases. Among healthcare information infrastructures, there were no specific BC ontology-based system approach to translating discoveries and trials into normal and regular care using semantic and logical models to build knowledge on which decisions and predictions are made within BC treatments and SEs.

The prompt progress in health information technologies and the considered growth of the worldwide Web consortium and health information standards dealing with biomedical modeling and computing protocols can overcome these challenges in health care especially in cancer and oncology research. On a large scale, with the increasing number of internet-connected healthcare users, companies use knowledge-based electronic commerce and structured financial services to maintain their competitiveness, especially within the global infectious pandemic crisis Covid-19 and its variants. Knowledge and Web-based information approaches have undergone major advances to how provide healthcare services and interact with RCTs being made within health organizations.

Based on these conditions and advances in cancer research and the treatment status of bladder malignancies, we propose to create a knowledge-based BC treatment infrastructure that exploits the most promising discoveries from different research bases, use RCTs rather than personal data to serve as evidence on which an assessment of possible complications and effects of a therapy protocol is provided. Moreover, this makes the best possible cancer care routine for all patients when building a clear semantic reasoning and knowledge-based treatment decisions.

2. Methods

2.1. Concept

The main objectives of the knowledge-based BC treatment effects and complications infrastructure (BCTECI) are the development of a common emerging knowledge core set and a unique information server for fundamental and clinical BC research by merging research on the patient's condition basics and the bio-structural level in research. Adding to that, the incorporation of health information standards to be used in knowledge model for sharing and exchanging or communicating relevant evidence extracted from RCTs ensures interoperability between systems. Moreover, RCTs were segmented into clear elements and classified within semantic concepts, and treatment protocol development was supported and the delay from reasoning to deciding about the effects was greatly shortened. Furthermore, the approach came up with a specific predictive feedback based on tailored secure evidence to fit the requirements of patients, and healthcare providers .

When used, this infrastructure approach orients oncologists, patients, and their caregivers to the best treatments with less complication risks adding to RCTs arguing this choice according to a specific BC tumor. On the other hand, to proceed the right reasoning and get the best decision making, both oncologist and patient need to meet certain standards and criteria as predefined in decision rules to let the inference engine apply the right logic queries or let the patient enter the RCTs. This eliminated many obstacles facing patients and doctors in choosing the most effective treatment with less complications and predict side effects adding to an easier mode of entering RCTs. Adding to that, accelerating RCTs evidence inclusion and the recruitment of patients into studies resulted in much faster and relevant answers to important scientific questions.

The specific aim of BCTECI is to gather relevant demographic, physical, prognosis and treatment data from patient cases in a safe way without information loss since the RCTs. Evidence and information needed for choosing the most appropriate possible treatment or for establishing the eligibility of RCTs were afforded by the local electronic patient registry details related to BC and directed by the oncologist. This removed the massive similarities between paper-based information and system registered data. For RCTs assessment and implementing evidence in BCTECI, current and standard tools and techniques were used in order to reach our presented aims. This meets the needs of many stakeholders in a simple user-oriented way. Also, it protects personal data and privacy.

The main activities of BCTECI focus on the treatment studies and their related SEs based on RCTs found in research supports. Treatment observations covered surgical and radiation therapy studies, chemotherapy and immunotherapy procedures, targeted therapy drugs and intravesical therapy effects. The whole spectrum of BC was integrated in a structured ontology model within the BCTECI. The outcome was promising and comprehensive. Within this knowledge-based approach, BC RCTs were assessed and integrated using a common semantic terms and reports, significantly improving decision making and predicting treatment efficiency and complications with its accuracy according to our work contribution described in (Fig. 1).

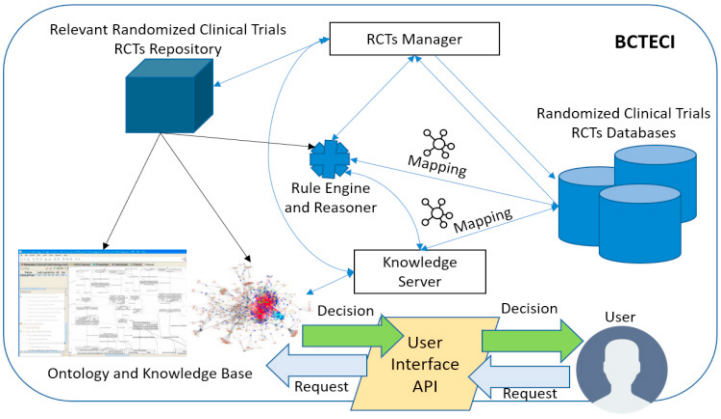

Fig. 1. The BCTECI evidence-based treatment outcomes approach supported by an ontology-based framework and RCTs management.

For easier use of RCTs, BCTECI suggests overcoming the time-consuming analysis and observations within electronic records' hunting by distant remote data entry directly in the system using a secure W3C connection which ensures the link with the corresponding predictive rule with reference to the assessed RCTs.

As shown in Fig.1, a prediction order is sent to the BCTECI reasoner which launches the corresponding treatment side effects rule. On the other hand, the included prediction criteria are compared to the relevant data registered in the RCTs classes repository. The request is assessed, and a decision knowledge is inferred. The result is then created to be completed by standard texts extracted from our predefined standards and regular rules class. Updates to the repository is done and the new decision returns to the repository as a new evidence and a new element of the RCT. Studies show that the dynamic knowledge-based decision models decrease error rates, as well as being faster than the existing paper-based algorithms or electronic cancer databases. The collection, generation and use of clean evidence from RCTs data was based on patients' cancer status and an oncologist supervision and approval.

2.2. Approach

Efforts to standardize BC treatment effects and complications based on RCTs included within an ontology model are particularly crucial for two reasons: First, the contribution does not cost money, but energy and no external funding required for a full conception and development of the BCTECI approach and multiple research teams will benefit from it in an easy way. Second, almost all the realizations took place locally and electronically. Moreover, considering information and knowledge modeling tools to create standardized evidence since RCTs promotes the development of electronic health standard specifications and treatment effects reference designs.

2.3. Search strategy and information methods protocol for the identification of studies

As a first intention, at the RCTs Manager Bloc (Fig.1), we adopted a systematic comprehensive search that included RCTs and data-based knowledge from PubMed/MEDLINE, Embase, Cochrane CENTRAL and the Allied and complementary medicine database (AMED) since their initiation. This study protocol has been registered on the international prospective register of systematic reviews network (PROSPERO) under the number CRD42021244668. We have organized this study, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols statement (PRISMA-P) [32].

Our review process was based on Cochrane guidelines for systematic reviews of interventions regardless time and language limitations. Terms and their combinations were searched following specific criteria including the ongoing trials too, about AEs of treatments applied to BC. Within some databases such as PubMed, we used the "related articles" function to refine the search. In the other hand, we manually searched in the retrieved-based studies' references as they were cited. An automatic search in Scopus and Web of Science was also applied within the checked electronic databases. We retained the most complete and updated studies, to which the outcomes are different in measures and time. This was to avoid the multiplicity and similarities included in reports with the same samples and results. All BC treatment SEs-related Knowledge and RCTs, were included. The detailed strategy for searching in PubMed/Medline is presented in Table 1. Moreover, we edited and carried out detailed search strategies for other electronic databases. Furthermore, we scanned RCTs registries including the ongoing trials, reference lists of relevant studies, conference papers and dissertations.

Table 1. Explicit Search Strategy sample using PubMed/Medline library.

Number	Search Terms/Combinations
1	(Bladder cancer) or (Tumor) or (Non-muscle invasive bladder cancer) or (Muscle invasive bladder cancer) or (Urothelial carcinoma) or (Transitional cell carcinoma)
2	Oncology
3	Or 1-2
4	((Chemotherpy) or (Cisplatin) or (fluorouracil (5-FU)) or (Mitomycin (MMC)) or (Gemcitabine) or (Methotrexate) or (vinblastine) or (doxorubicin) or (Adriamycin) or (paclitaxel))
5	((Immunotherpay) or (BCG) or (Atezolizumab (Tecentriq)) or (avelumab (Bavencio)) or (Nivolumab (Opdivo)) or (pembrolizumab (Keytruda)) or (Enfortumab vedotin (Padcev)))
6	((Surgery) or (Transurethral resection of bladder tumor (TURBT)) or (Cystectomy) or (Partial cystectomy) or (Radical cystectomy) or (Incontinent diversion) or (Continent diversion) or (Neobladder)

7	((Targeted Therapy Drugs for Bladder Cancer) or (Erdafitinib (Balversa)) or (FGFR inhibitor))
8	((Radiation therapy) or (External beam radiation therapy) or (chemoradiation))
9	((Intravesical therapy) or (drug))
10	((Treatment) or (therapy) or (intervention))
11	Or 4-10
12	(Side effect) or (adverse event) or (complication)
13	Or 12
14	((Randomized controlled trials) or (clinical trial) or (study)) or ((random) or (blind) or (allocation) or (control))
15	Or 14-15 Or 3 and 11 and 13 and 15

2.4. Data collection and analysis

For our study selection we used the EndNote X7.8 as a tool to import our identified reports and performed data deduplication on our gathered information from previous studies (literature). Among the authors, two independent researchers browsed the content of all relevant studies and scan their taxonomy, abstracts, location ID and titles to extract the required data from the included RCTs. Furthermore, based on our predefined eligibility criteria, unassociated contents were excluded from the identified studies. Then, full text evaluation was processed for eligibility and inclusion according to defined criteria. Both researchers extracted, selected, and evaluated the quality of the recorded studies, independently, using the recommended tool of Cochrane risk of bias (RoB 2) within the included RCTs. Adding to that, PICOs were used based on the consolidated standards of reporting trials (CONSORT). Any conflicting views, disagreement or inconsistencies were resolved by consensus with the help of another researcher which is the adjudicating senior author to reach a final decision after discussion. The study selection process obeys to PRISMA guidelines.

Moreover, both researchers extracted data from the selected RCTs studies, using an excel standardized pre-created data gathering form. Any conflicting views, disagreement or inconsistencies were figured out and resolved through arbitration by a third author and a decision was taken by consensus at the end of the discussion. The extracted data consisted of items related to treatment regimen, AEs and SEs, outcome measurements, intervention and controls details, the trial design, age, results, follow-up information, complication, conflict of interests, reference information, physical characteristics of patient, authors information, exclusion and inclusion indicators and other interesting outcomes and details. In case of missing information or insufficient data, we approached the original primary RCTs authors for additional details.

2.5. Study quality and risk of bias assessment and statistical analysis

The evidence assessment quality was appraised by two researchers independently. The adopted methodology involved the grading of recommendations assessment, development, and evaluation (GRADE) approach. We used the GRADEproGDT guideline development tool, within the included studies, to rate the quality assessment as high, moderate, and low quality for the certainty of evidence and strong and weak for the strength of recommendations [33]. The identified risk of bias related to each included RCTs was assessed using the recommended tool of Cochrane risk of bias (RoB 2) and the PICO question model based on the consolidated standards of reporting trials (CONSORT). The evaluation was based on seven criteria to which each aspect was categorized as unclear, high or low risk of bias. Any discrepancies will be ruled and managed by a third researcher through adjudication.

For statistical meta-analysis, we used the Cochrane collaboration's software Review Manager (RevMan 5.3) which uses the Cochran–Mantel–Haenszel test method (CMH) to carry out statistical analysis. Treatment SEs of continuous data was considered and estimated as a standardized mean difference and dichotomous data as a risk ratio, while 95% confidence intervals were provided. A p-value ≤ 0.05 was considered statistically significant which indicates strong evidence against the null hypothesis (no significant difference) to be rejected and the alternative hypothesis (difference is anticipated) is retained which states that the results are significant in terms of supporting the investigated study and 95% confidence intervals (CI) were provided. The CMH-χ^2 -test was used to evaluate statistical heterogeneity within the used studies and a p-value<0.1 of significance. However, the Higgins I2 statistic was used to determine and quantify the heterogeneity across the included RCTs and research results. Moreover, it was used to examine the null hypothesis. When $I2 \leq 50\%$, homogeneity is detected, and a fixed-effects model is applied, and a meta-analysis is undertaken. However, $I2 > 50\%$ suggests a significant heterogeneity and a random-

effects model meta-analytical technique is used with subgroup analysis to identify and specify this heterogeneity within outcome results. Otherwise, we will present a detailed summary to report the obtained outcome results in the future. When heterogeneity is significantly detected between the included RCTs, we perform subgroup analysis to find the reasons behind this heterogeneity in keeping with the differences in BC treatment types and regimens, comparators, patient information, outcomes, and SEs grades and occurrence. We carried out a sensitivity analysis to evaluate the robustness and reliability of the obtained results and conclusions by eliminating low quality studies presenting high risk of bias. The Egger regression test graph and Begg funnel plot graph is performed if the included studies dealing with outcome indicators exceed 10 studies, to detect and identify reporting bias [34][35]. We appraised the quality of evidence and the level of confidence using GRADE technique. Any divergence was solved with the help of the third researcher through arbitration.

2.6. Knowledge representation

Knowledge representation and ontology design were established to provide a common model and ensure that data and applications are sharable through interoperability. To simplify CRFs, our research team identified common data taxonomy and terminology based on SNOMED-CT, ICD-11 and LOINC comprehensive clinical terminology for RCTs to be integrated within our ontology. A rule-based treatment protocol was created for electronic protocol assessment that enables oncologists and patients to be on the front end, to see how the RCTs will be effective in the prediction according to the main problematic of complications. For our ontology development we used OWL2-DL as a standard language as suggested by the W3C. By establishing class hierarchy, we represented concepts and their relationships captions as datatype and object properties. SWRL (the Semantic Web Rule Language) and SQWRL (the Semantic Query Web Rule Language) were used to build semantic and logic rules including descriptive logic models. These queries verify and validate the restrictions representing knowledge, evidence and RCTs data about BC treatment outcomes. The main classes are treatment characteristics, RCTs evidence, BC malignancy and patient physical status. Instances were used to detail our concepts in special characters. Our knowledge model was built within the Protégé semantic development tool. It contains Pellet 2 reasoner which infers knowledge and decisions adding to the validation of the ontology through criteria assessment : Taxonomy, consistency, and inference. The included relevant RCTs were then encoded within our knowledge graph to serve as evidence in future clinical decision making. Hence, oncologists, urologists and clinicians could build knowledge-based protocols through our represented and modeled elements. For knowledge representation, we used XML and RDF schemas.

More than 3000 hits of RCTs were crawled since different databases. These multiple active cases report BC treatment trials and their outcomes as common characteristics contents which were used and included within our approach to develop a generic clinical trial-based evidence model. The most omnipresent classes of knowledge that were obtained: eligibility, efficacy, risk of bias, safety and complications, consents, outcomes, and bladder malignancy specificity. The indicated assessment elements were created from the detailed relationships of concepts within RCTs and logic/semantic models.

2.7. Eligibility Analysis/Eligibility criteria for study selection and inclusion

Initially, the criteria for inclusion and exclusion of studies were evaluated as part of the initial attempt to develop standards for RCTs eligibility. Distinct and contradictory requirements were detected and categorized into a multi-level eligibility hierarchy classes with top nodes: Patient physical Status , BC characteristics, Tumor stage and Treatment Protocol. In this study, all RCTs involving BC treatments and studying or reporting the effectiveness and SEs of the prescribed BC treatments, were included. No limitations related to publication time or language were involved in the criteria. Only RCTs were taken into consideration, other studies were excluded. We included all the involved studies that describe the applied BC treatments as interventional management and focus on their related AEs and SEs severity grades. Furthermore, any other treatment of BC different from the performed one was used as a comparator including SEs. On the other hand, we avoided any use of studies implicating the same control treatments/procedures and the same AEs severity grades as we identify as not allowed. Only patients within studies, meeting the confirmed clinical diagnosis criteria of BC and observed with treatment AEs or SEs severity grades related to their clinical state, were included in this study without racial, gender, age and regional limitations or BC

duration. Our primary outcomes included: (i) the treatment SEs' prediction and detection rate using knowledge-based reasoning in relation with BC including non-muscle invasive BC (NMIBC) and muscle invasive BC (MIBC); and (ii) overall survival and progression-free survival within AEs' severity grade. While secondary outcomes were SEs management, preventing the recurrences and occurrence of SEs risks and the impact on quality of life.

We have defined the concept of a clinical trial case to help determine eligibility and its impact in predicting treatment effects and complications. A clinical trial case could be considered as the process by which patients are classified into an approximatively similar cases, based on patient's medical history, BC characteristics and treatment reactions. Diagnosis, prognosis, and therapy protocols are suggested to be relative so that these conditions are similar in all patients. This enabled to emerge inadequacies and relevant details which makes the difference between a patient case to another one regarding sensitive information about patient's specific effects and complications. It is like a white clear space in which a number of black spots appear and show up (complication prediction results).

3. Results and Discussion

The number of studies investigating the effectiveness and impact of BC treatments for patients with NMIBC and MIBC has increased over the last years, as is the number of patients required per study. A multitude of RCTs have been carried out to evaluate the efficacy and SEs of the applied treatments in patients with BC at different stages and types of the cancer. Adding to that, AEs grading, and riskiness were evoked in several research work. However, no systematic review or study was conducted at the conceptual and semantic level to gather and investigate this evidence. Hence, this systemic review was carried out within our study, to investigate the effectiveness, efficacy, and SEs of BC treatments for NMIBC and MIBC. This is to provide an assured and secure evidence-based treatment for research studies and BC clinical practice to serve as reference and recommendation. This study is anticipated to provide significant evidence about grades and aspects of SEs in treatments for patients with NMIBC and MIBC.

Detailing risk factors and estimating both impact and possible damages enhanced SEs management and improved treatment prescription. This comprehensive study gathered evidence and mainly used the Cochrane risk of bias RoB 2 and GRADE tools for quality assessment of the included RCTs. This study may present limitations related to the methodological quality of included RCTs, but no restrictions were presented within this work.

Within our BCTECI approach, a knowledge and ontology-based system supported 81% of the inclusion and the use of specific relevant RCTs available in many different medical studies consortiums. Research teams cooperate to improve the management of the RCTs for decision making tasks. Here, we encrypted RCTs plans by performing semantic model schemas between the extracted RCTs repositories from the available databases and our ontology. We are improving our approach to capture logic restrictions that are more complex. We are planning to a direct mapping to electronic data repositories. This enhances the quality and quantity of queries on RCTs elements. Adding to that, developing a graphical user interface API conceals the intricacies of knowledge models and allow for directed knowledge acquisition. Clinical decision-support systems providing clinical advice at the hospital are based on formal guideline models like PROforma [36] and EON [37]. The used formalisms differ in various ways, namely the domain specialty, semantic representation and structure and complication in reasoning. The advising model affords a special manner to describe knowledge within clinical guideline publications. In these approaches, compared to the needs with various RCTs management system that we outlined before, the semantic integration specifications in such software are substantially simpler. However, this was included in our work, demonstrating the predictive potential of the ontological model from a small cohort of RCTs.

More than 600 semantic and logic rules were launched within our system to generate conclusions about treatment SEs prediction. With this investigation being extended to a whole 3,453 RCTs including treatments as Chemotherpy (Cisplatin, fluorouracil (5-FU), Mitomycin (MMC), Gemcitabine, Methotrexate, vinblastine, doxorubicin, Adriamycin, paclitaxel), Immunotherpay (BCG, Atezolizumab (Tecentriq), avelumab (Bavencio), Nivolumab (Opdivo), pembrolizumab (Keytruda), Enfortumab vedotin (Padcev)), Surgery (Transurethral resection of bladder tumor (TURBT), Cystectomy, Partial cystectomy, Radical cystectomy, Incontinent diversion, Continent diversion, Neobladder), Targeted Therapy Drugs (Erdafitinib, Balversa, FGFR inhibitor), Radiation therapy (External beam radiation therapy, chemoradiation), Intravesical therapy, a significant change in the complication rate was observed. High fever, chills and fatigue were noted in 38% of immunotherapy patients more than those who received radiation therapy 24%. Erectile dysfunction increased from an incidence of 27 to 32% for all treatments. Major hematuria

occurred in 64% of Surgery patients compared to Chemotherapy procedures. Anemia and/or kidney damages as a result of chemotherapy was observed in 34% of the patients, while life-threatening immunotherapy BCG sepsis was found in 12%, cystitis occurred in 29% and itching and skin problems in 48%. The incidence of ureteral infection is 42%, bruising 36% and trouble breathing 9% in Targeted therapy more that radiation therapy. Mild faint remained particularly unchanged. The total heterogeneity was about I2=73% of significance, and the whole system performance and outcomes presented 87% of relevance and consistency compared to real reported results. Some of the differences were large, for example with a median difference of 26% (95% CI 15 to 35) there was a significantly higher estimated prediction of grade 4 side effects in favor of chemotherapy plus radiation therapy versus chemotherapy alone. All median differences were in favor of the first intervention listed in pairs. The use of a standardized taxonomy and regular terminology insured the interoperability within BCTECI.

Compared to our approach, several projects tried to automate certain aspects of RCTs management, such as the Asgaard approach [38], which represents protocols using an intention-based design and a rationalized specification modeling. FastTrack [39], and the Clinical Data Interchange Standards Consortium [40] which is in collaboration with HL7 and TrialBank [41] use a formal methodology to manage and record data from RCTs and to develop new interoperability standards within RCTS. It still doubtful how these models will affect approaches developed outside the medical organizations. Furthermore, the majority of available models are insufficiently described in electronic knowledge formalisms for specifying annotations and constraints, which are at the heart of RCTs procedures. However, our approach made it possible to manage RCTs, predict side effects and grades using the OWL2 standard with a unified medical taxonomy and consistent reusable inference rules through knowledge-based ontology model.

4. Conclusion

Adding to our relevant RCTs assessment strategy, methods and tools explained in this paper, our approach uses semantic web technologies to make it easier to combine different RCT resources that share the semantics of relevant trials rather than formalisms of description and representation. The semantic web organizations have made various attempts to combine disparate information resources. Our BCTECI system can comply with future advances and can be used within different RCTs repositories thanks to ontology characteristics and health interoperability standards.

We are currently working with cooperative research teams, oncology, and urology specialists to standardize the most predictive criteria element in RCTs focusing on treatment outcomes and their semantics. We will keep on developing common knowledge details for BC and build models for representing and sharing wider RCTs. This study is being continued to experiment and evaluate our approach on the basis of multiple RCTs focusing on specifying BC treatment outcomes.

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