Automated Tumor Name Standardization in the NIH Clinical Trials Registry Using the CANTOS Pipeline

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**ABSTRACT**

**Objective:**

To identify and standardize tumor names from the National Institutes of Health's (NIH) clinical trials registry (ClinicalTrials.gov) according to the tumor terminology in the World Health Organization (WHO) Tumor Classification System (WHO database) and the National Cancer Institute Thesaurus (NCIt database).

**Materials and Methods:**

We developed CANTOS (Clinical Trials Automated Nomenclature and Tumor Ontology Standardization), a computation pipeline to identify tumor names from the clinical trials registry and standardize them according to nomenclatures in the WHO and NCIt databases. CANTOS implemented twelve standardization methods based on text matching and embedding. We tested the accuracy of these methods on a subset of tumor names from the clinical trials registry against the 5th and all editions (3rd, 4th, and 5th) of the WHO database. We limited the evaluation to the WHO database, which is considered the gold standard for tumor nomenclature.

**Results:**

Text-matching methods achieved accuracies ranging between 21.7% -30.5% for the 5th edition and between 22.7%-32.4% for all editions. In contrast, text-embedding methods achieved accuracy between 60.5%-65.6% for the 5th edition and 63.5%- 68.5% for all editions, significantly outperforming text-matching methods. The highest accuracy was achieved by the method LTE-3+Euclidean Dist, which mapped tumor names in the registry to the nearest term from the WHO database using Euclidean distance in the embedding space with accuracies of 65.6% for the 5th edition and 68.5% for all editions.

**Discussion and Conclusion:**

CANTOS provides a mechanism to identify and standardize tumor names from the clinical trials registry, enabling users to integrate this data with external biomedical databases for downstream analysis.

**INTRODUCTION**Cancer is a significant global health issue and the second leading cause of death in the United States [[1]](https://paperpile.com/c/NPPxEM/Weij). In 2024, over 2 million new cancer cases and 611,720 deaths are expected in the U.S. alone [[2]](https://paperpile.com/c/NPPxEM/6kRx). While pediatric cancer survival rates have improved to 80% over the last five decades [[3,4]](https://paperpile.com/c/NPPxEM/tUKD+FRbF), which can primarily be attributed to successes in the treatment of common childhood hematological malignancies such as acute lymphoblastic leukemia [[5]](https://paperpile.com/c/NPPxEM/68hp), unfortunately this success is not uniformly shared [[6]](https://paperpile.com/c/NPPxEM/NRZI), and certain cancers, particularly those of the brain and nervous system [[2]](https://paperpile.com/c/NPPxEM/6kRx), remain difficult to treat.. Pediatric cancers are rarer than adult cancers and face unique challenges in clinical trials, including limited therapeutic agents, difficulty recruiting diverse populations, and tumor heterogeneity [[7,8]](https://paperpile.com/c/NPPxEM/Lq9U+5cZt). Therefore, to understand the therapeutic landscape of adult and pediatric tumors, it is critical to extract and analyze data from various biomedical databases, particularly from the NIH’s Clinical Trials Registry (ClinicalTrials.gov, CTR) which contains data from over 482,529 research studies across all 50 states in the US and 223 countries [[9]](https://paperpile.com/c/NPPxEM/hYaH). While the CTR has established protocols and guidelines for data the submission process, the data with respect to tumor names contained in the "conditions" data file (conditions.txt) of the CTR database contains inconsistencies in the form of extraneous information, typographical errors, missing values, non-standard nomenclature, etc, which create barriers for data integration and downstream analysis of this data. Although the CTR mandates standardized terminology like Medical Subject Headings (MeSH) [[10]](https://paperpile.com/c/NPPxEM/Hrsy), these terms often fail to capture the specific details of many tumor types outlined in the conditions data file. In supplemental table S1, we provide examples to compare the differences between the terms in the condition file and the MeSH terms. Thus there is a need to standardize the tumor names in the CTR with respect to standardized nomenclature from the WHO Classification of Tumors system (referred to as the “WHO database” in the rest of the paper, <https://tumourclassification.iarc.who.int/welcome/>) or National Cancer Institute Thesaurus (referred to as the “NCIt database” in the rest of the paper <https://ncithesaurus.nci.nih.gov/ncitbrowser/>).

To this end, we developed a computational pipeline CANTOS (Clinical Trials Automated Nomenclature and Tumor Ontology Standardization) that standardizes tumor names in the CTR’s “conditions” file using methods based on text-matching (based on edit distances) and text-embedding derived from OpenAI’s Large Language Models. This pipeline maps tumor names to their standardized counterparts in the WHO and NCIt databases. Standardizing these tumor names in the CTR enables integration of this data with other biomedical databases, such as Open Targets (OT, <https://www.opentargets.org/>) and Illuminating the Druggable Genome (IDG, <https://druggablegenome.net/>) , facilitating a more comprehensive understanding of tumor biology, drug-targets, and therapeutic agents.

**METHODS**

In this section, we discuss the design and methods implemented of the computational pipeline CANTOS. The key tasks performed by CANTOS are divided into two major steps: (i) identification of tumor names from CTR and (ii) standardization of CTR tumor names. CANTOS takes the condition names from the CTR as an input along with the standardized tumor names from the WHO and NCIt databases. After the tumor name identification in the first step, CANTOS iterates through the standardization step twice as we had to consider the editions of WHO database to use in the pipeline.

The WHO database is considered the gold standard for tumor nomenclature and it has been updated over the years due to which there are multiple versions of this database. Thus, we considered the 5th, 4th, and 3rd editions of the WHO database which are publicly available online as a reference for standardization. During the first iteration of the standardization step, we ran CANTOS with only the latest version of WHO database (5th edition) and then on the second iteration we ran it with all editions (3rd , 4th and 5th) of the WHO database. The purpose of this was to standardize the tumors from clinical trials with respect to two variations of the WHO database: the latest (referred to in this text as the WHO database 5th Edition) and the combined editions of the WHO database (referred to in this text as the WHO database All Editions). During each of these iterations of the pipeline, the tumor names from the CTR were also standardized with respect to the NCIt database.

**Data Availability**

Users can download the data used in this paper from the CTR website (<https://clinicaltrials.gov/>) [[9]](https://paperpile.com/c/NPPxEM/hYaH), Clinical Trials API or from the Aggregate Analysis of ClinicalTrials.gov-Clinical Trials Transformative Initiative (AACT-CTTI) website (<https://aact.ctti-clinicaltrials.org/download>). We downloaded a copy of the database from the ACCT-CTTI website on August 22, 2023 which is available as a zip file titled “20230822\_export.zip” under the section titled “Monthly Archive of Static Copies”. The ACCT-CTTI website is updated daily with contents from ClinicalTrials.gov and a static database is made available at the start of each month.This database contains information about all the studies registered in the CTR and particular details of clinical trials such as its experimental design, conditions, interventions etc are presented in separate pipe-delimited text files which are contained in the zip file. In Supplementary File S2, we outline the process through which the user can download the dataset used in this study.

**Identification of Tumor Names from CTR**

The CTR contains information about various aspects of a clinical trial, such as outcomes, interventions used, conditions (diseases) studied, design of experiments, sponsors of the studies, etc. This information is presented to the public in individual text files. Each text file contains the National Clinical Trial Identification Number (NCTID), which serves as the unique identifier (foreign key) for that clinical trial. The NCTID allows one to reference a particular clinical trial and aggregate various information associated with it, which is stored in various text files across the database. In this study, we selected the conditions ("conditions.txt" or conditions file) and interventions ("intervention.txt" or interventions file) files, which contain information regarding conditions and drugs used in each clinical trial study. The conditions file contains 801,197 records and is annotated with the following fields: "*id*," "*nct\_id*," "*name*," and "*downcase\_name*." The "*id*" field represents the identification number for that record within the conditions file, whereas the "*nct\_id*" is the foreign key for that record. The "*name*" and "*downcase\_name*" fields contain names of the conditions studied in a specific clinical trial study, with the "*downcase\_name*" containing the condition name in "*name*" in downcase format. We identified 105,483 unique conditions (by uniqueness of strings) in the conditions file.

The conditions file does not categorize the condition names into specific subtypes or classes, consequently the tumor names contained in the file are not easily identifiable and need to be extracted. Furthermore, we are focused on extracting tumor names that are associated with a therapeutic agent (i.e., has a drug-target) registered in the CTR, so that it enables us to obtain a clear view of the therapeutic and drug-target landscape for a given tumor in future studies. To address this need , we designed the CANTOS pipeline to extract tumor names from the rest of the conditions, and then annotate each unique tumor as pediatric or adult tumors (Figure 1). The tumor name identification step implemented by CANTOS is segregated into three phases.

In Phase 1, CANTOS focused on extracting conditions names (consequently tumors names) that are associated with a therapeutic agent (i.e., has a drug-target) registered in the CTR. To achieve this, CANTOS subsets the condition names in the conditions file with the types of drugs registered in the interventions file. The intervention file has 786,898 records and is annotated with the following fields: "*id*," "*nct\_id*," "*intervention\_type*", "*name*," and "*description*." The "*id*" field represents the identification number for that record within the conditions file, whereas the "*nct\_id*" is the foreign key for that record. The "*name*" and "*description*" fields provide names and details regarding the interventions used in that particular clinical trial, and the "*intervention\_type*" field classifies the interventions into one of the eleven distinct intervention types listed in Supplementary Table S3. CANTOS extracts conditions names (consequently tumors names) associated with an associated therapeutic agent with a drug target, by first joining the intervention file with the conditions file using the foreign key NCTID ("*nct\_id*") and then filtering the file for interventions belonging to the following intervention type: "*Drug*", "*Biological*", "*Combination Product*", and "*Genetic*". We selected the condition names associated with these intervention types to ensure that there is a corresponding drug-target for any tumor names that are contained in the conditions names extracted by CANTOS. Tumor associated interventions belonging to these intervention types would provide the necessary insights required by researchers for studying the therapeutic and drug-target landscape of a given tumor. After filtering based on the specified intervention types, CANTOS extracted 50,410 unique conditions names which were then used as an input for tumor identification in Phase 2 of the pipeline. The tumor extraction process is visualized as Phase 1 of the pipeline in Figure 1.

**Figure 1**: **Tumor extraction and annotation pipeline**

In Phase 2, CANTOS identified tumors from the rest of the conditions (Figure 1, “Phase 2”) using two independent protocols.The first protocol consisted of checking if each condition name contained a tumor key word listed in Supplemental Table S3. If the condition name contained a tumor keyword, that condition was annotated as a potential tumor.

The second protocol in Phase 2, CANTOS matched each of the conditions in the CTR to the tumor names listed in the 5th edition (latest) of the WHO database using a fuzzy string match algorithm. If a condition name from clinical trials exactly matched a term in the WHO database, it was annotated as a tumor. If the condition name did not match to any tumor within the WHO database, we performed a fuzzy (approximate) match with the condition name with each term in the WHO database. This was done by computing the generalized Levenshtein edit distance of the clinical trials disease to each WHO database term. The fuzzy matching using generalized Levenshtein edit distance was implemented using the agrepl function in R [[11]](https://paperpile.com/c/NPPxEM/rIfO) and the maximum distance was set to 0.2. If there was at least one WHO database term within this maximum distance, that clinical trial disease was flagged as a potential tumor. Once a clinical trial disease was flagged as a potential tumor by either of these two protocols, we manually validated the findings to confirm if conditions marked as potential tumors were indeed a tumor.

After the manual validation step in Phase 2, a total of 13,230 unique (by string uniqueness) tumor names were extracted from the CTR. In Phase 3 of the tumor identification step, CANTOS aimed to further identify which of these extracted tumor names were pediatric (Figure 1, phase 3”) by implementing a similar fuzzy string match algorithm as in phase 2, by comparing them to the pediatric tumor names listed in the 5th edition of the WHO database (instead of the entire 5th edition of WHO database). Once the tumors were annotated as pediatric or adult by CANTOS, we manually validated the findings. If the tumors were marked as pediatric by manual validation, we manually added a citation from peer reviewed literature, governmental websites or articles posted by research institution

where it states that the tumor in question is a pediatric tumor. If the tumor in question is found in the WHO database, we simply state “Listed in WHO Ped Tumor” in place of providing a literature reference. Out of the 50,410 conditions, 13,230 conditions were identified as tumors among which 6324 were determined to be pediatric tumors. These annotations are stored in the supplementary file S5 titled: “tumor\_annotated\_adult\_ped.csv”.

A cursory analysis of the identified tumor names revealed various sources of discrepancy such as typographical errors, extraneous information, missing values, drug names entered instead of condition names, multiple tumor names etc. Furthermore, many tumor names in the disease file did not follow standardized nomenclature from the WHO or the NCIT databases. With these unstandardized tumor names, it becomes challenging to integrate the tumor name data from CTR to other biomedical databases, such as IDG or OT. These discrepancies also prevented manual annotation of these tumor names as pediatric or adult tumors, and consequently 144 clinical trials tumors were annotated as “DA” (Do not Annotate) in the field designating them as pediatric tumor (“PedCanTumor) in the supplementary file S5. Supplementary Table S6 outlines some of these common discrepancies associated with tumor names. Due to various sources of discrepancies in the tumor names in the CTR, there is a need to standardize them so these tumors can be linked to external databases to draw further insights about associated drug targets and currently available FDA-approved drugs. The standardization methods implemented by CANTOS are discussed in the following section.

**Standardization of CTR Tumor Names**

We implemented various methods in CANTOS to standardize the tumor names in the CTR. These methods are based either on text-matching (edit-distances) or text-embedding. CANTOS also implements methods that combine unsupervised clustering along with text-matching and text-embedding to standardize the terms in CTR. In total, we implemented 12 methods and tested their performance accuracies which are discussed in the results sections. In the following subsections, we will first discuss each of these text-matching and then text-embedding based standardization methods.

*Text Matching Technique: Closest match using edit distance:* The goal of standardizing tumor names from the CTR to their corresponding WHO or NCIt terms is to accurately align each unstandardized term with a standardized equivalent from the WHO or NCIt database, ensuring that the original meaning of the CTR term is preserved in the mapped term. Edit distances offer a way to compare the similarity between two sets of texts (referred as strings in the rest of the manuscript). Edit distances can be based on the minimum number of edit-operations (deletions, substitutions, insertions, etc), q-grams or heuristics that are required to transform one string into another. The larger the edit distance between two strings, the further apart the strings are; thus, two strings with minimal edit distance could potentially convey the same meaning. There are several methods to compute edit distances between strings; in this paper, we use normalized Levenshtein distance, Jarro-Winkler distance, and cosine distance, which are commonly used edit distances. An example of how edit distances can be used to compare strings is discussed in supplementary file S7. Following are brief descriptions of each method.

*Normalized Levenshtein distance*: Levenshtein distance between two strings is defined as the minimum number of single character edits which include insertions, deletions or substitutions required to transform a string to its target string. The Levenshtein distance between two strings is not normalized. To normalize them, we divide the Levenshtein distance by the length of the longest string, so that we get a distance in the interval [0,1]. By normalizing the Levenshtein distance, we can compare the dissimilarity between a string and multiple target strings on the same scale ([0,1]). Furthermore, we can also define the similarity between two strings S1 and S2 as follows:

In the above equation , |S1| and |S2| represent the respective lengths of strings S1 and S2 between which we are computing the normalized Levenshtein distance. We calculate Levenshtein distance using the stringdist library in the R programming language [[12,13]](https://paperpile.com/c/NPPxEM/MKyW+hon3) . Following the calculation of the Levenshtein distance, we compute the normalizing factor (i.e. divide the Levenshtein by the longest string size) for distance between each pair of strings and normalize the Levenshtein distance.

*Jarro-Winkler distance*: The Jarro-Winkler distance is a normalized edit distance between two strings. It is a variant of the Jarro similarity measure which is defined as follows between two strings S1 and S2 respectively:

Where S1 and S2 are lengths of the strings S1 and S2 respectively , m is the number of matching characters and t is the number of transpositions. It should be noted that when estimating ‘m’, each character in S1 compared to the characters in S2, and match is counted only when the characters are the same and if the characters are within a certain distance of each other typically defined as half the length of the longer string, rounded down, minus one, i.e. .

The Jarro-Winkler similarity measure builds on top of the Jarro similarity measure and introduces two more parameters for rewards and favorable scales the Jarro similarity score if the two strings share similar prefixes. The Jarro-Winkler similarity is defined as follows:

Where *l* is defined as the length of the common prefix at the start of the string (maximum of 4 characters) , whereas *p* is a scaling factor that rewards the score for having common prefixes. Typically *p* is set to 0.1 and should not exceed 0.25 (or ¼ as the maximum length of prefix being considered is 4). With the above definition of Jarro-Winkler similarity, the Jarro-Winkler distance is defined as follows:

We calculate the Jarro-Winkler distance using the stringdist package in the R-programming language.

*Cosine Distance***:** To define cosine distance , we first need to establish the concept of cosine similarity. For two non-zero vector vectors, cosine similarity is defined as the dot product of the two vectors divided by the product of their lengths. Cosine similarity ranges from [-1,1], with -1 representing total opposition, 0 representing complete dissimilarity, and 1 representing full similarity between the vectors. Cosine similarity between two vectors A and B is defined as follows:

However, to use cosine similarity in the context of strings, the vectors A and B represent the frequencies of unique words in strings S1 and S2. Since frequencies cannot be negative, the cosine similarity ranges between [0,1]. Thus, there is no need to normalize this metric, and cosine distance is defined simply as

We calculate the cosine distance using the stringdist package in R. Based on the three edit distances, CANTOS computed the pairwise distances between each tumor name identified in the CTR and the standardized tumor terms with respect to the WHO (5th edition and all editions) and NCIT database. For each CTR tumor name, CANTOS selects the nearest standardized terms under each edit distance. If more than one term qualified as the closest term, CANTOS reported them all by separating individual terms with a semicolon.

***Text Matching Technique: Edit Distance combined with Affinity Propagation Clustering***

CANTOS implements another set of standardization methods that are based on edit distances and clustering techniques. These methods consist of a clustering step which is followed by a mapping step. To form the clusters, CANTOS applied affinity propagation (AP) clustering, where the divergence matrix is computed by calculating the pairwise edit-distance between the CTR tumor names and standardized terms from the WHO and NCIt databases. CANTOS computes three edit-distance based divergence matrices using normalized Levenshtein distance, Jarro-Winkler distance, and cosine distance. Using each of these divergence matrices, CANTOS runs the AP clustering and forms three sets of clusters. We selected the AP algorithm for cluster as it automatically determines the number of clusters instead of requiring the number cluster (which is not known to us) to be a user-defined hyperparameter. Unlike other clustering algorithms, AP is also not dependent on the initialization conditions and is deterministic [[14]](https://paperpile.com/c/NPPxEM/OxXw). AP works by recursively passing real-valued messages between each data point until they converge, and based on these converged values, the algorithm establishes the clusters and assigns each cluster an "exemplar data point" which serves as an ideal representative of that cluster [[15]](https://paperpile.com/c/NPPxEM/ZrGQ). Furthermore, AP clustering methods have shown success in clustering textual data [[16,17]](https://paperpile.com/c/NPPxEM/vxqy+FX6U). Once the clusters were computed using AP, CANTOS performs a cluster size analysis to check if there are any clusters which are large and may contain members that should not belong together. This was done by determining the median cluster size and clusters larger than the median cluster size were identified and designated as large clusters. On each of these large clusters, CANTOS performs nested AP clustering until their sizes drop below the previously determined median cluster size or if AP clustering algorithm converges, and no more new clusters can be performed.

CANTOS then checks for outliers within each cluster using isolation forest and local outlier factors (LOF) algorithms. If a data point within a cluster is determined to be an outlier by either of the algorithms, then that data point is removed from its original cluster and reassigned as a new cluster with just that data point. CANTOS implements isolation forest using the R isolation.forest package [[18]](https://paperpile.com/c/NPPxEM/5rKu). The number of trees (ntrees argument) is set to 100 as recommended by Lie et al.2008 [[19]](https://paperpile.com/c/NPPxEM/vpqB) in their original introduction of the isolation forest algorithm and the dims argument to 3, as suggested for numeric datasets in the package documentation[[18]](https://paperpile.com/c/NPPxEM/5rKu). The standardized outlier scores are calculated for each data point within a cluster. An outlier score close to 1 indicates the data point is a likely outlier, while an outlier score close to 0 indicates the data point is likely a member of the cluster and not an outlier. The CANTOS pipeline uses an outlier score of 0.5 as the threshold and any data point with an outlier score greater than 0.5 is deemed as an outlier. Similarly, CANTOS uses the lof function within the dbscan package [[20]](https://paperpile.com/c/NPPxEM/ibnD) in R to compute the LOF values to determine outliers in each cluster. The LOF value for a data point *p* is defined as the local reachability density *p* and the local reachability density of “minPts”-nearest neighbors of *p* [*[21–23]*](https://paperpile.com/c/NPPxEM/Yd50+tkjs+YhfR). The variable “minPts” is a user defined hyperparameter and specifies the minimum number of nearest data points around *p* that need to be considered for calculating LOF value. An LOF value close to 1 indicates that the data point *p* is in a region with a relatively uniform density, whereas a LOF > 1 indicates the data point *p* has a lower density than its neighbors and is likely an outlier [[23]](https://paperpile.com/c/NPPxEM/YhfR). To compute the LOF values for each cluster member in each cluster, the CANTOS pipeline requires the users to define the minPts parameter. We set minPts to be integers ranging from 2 (clusters need to have more than one element to have an outlier) to . Iterating through each value of minPts, CANTOS then computes LOF values for each cluster element and then computes their median LOF value. If the median LOF value is above 1 for a data point *p* in a cluster, then it is designated as an outlier.

Upon completing the outlier analysis, CANTOS implements the mapping step where each cluster member is mapped to a standardized term. To achieve this, CANTOS iterates through each cluster and identifies the closest standardized term from the WHO (5th edition and all editions) databases based on the edit distance implemented in the pipeline. If a majority of the tumor names in a cluster are close to a specific standardized term, then all the tumor names are mapped to that standardized term. In case, there is a draw, where two or more standardized terms are equally represented in a cluster, then each tumor name within that cluster is assigned to its closest (based on the edit distance used so far) matching standardized tumor name. The text-based matching pipeline is described in detail in supplementary figure SSSSS and summarized version is shown in figure 2. The following section will discuss the pipeline that standardizes the clinical trial tumors based on text-embeddings.

**Fig 2: Text match and text embedding pipeline summary.**

***Text Embedding Analysis: Closest match in Embedding Space***

The methods in the previous section employed edit distances to compare texts. These methods primarily focus on syntactical differences to quantify the differences between texts. In this section, the standardization methods deployed by CANTOS are based on text embeddings (or word embeddings), which can also be used for comparing texts. Text embeddings are low dimensional numeric vector representations of unstructured text data. Unlike edit distances, text embeddings focus on capturing the semantic and contextual meaning of the input text they encode; consequently, in the embedding vector space, texts with similar meanings should have embeddings close to each other and texts which differ in meaning should be further apart [[24–27]](https://paperpile.com/c/NPPxEM/SePY+AIyW+WbHn+bKvK). Text-embeddings have been used in various applications such as developing search engines [[28,29]](https://paperpile.com/c/NPPxEM/fu7E+8uDZ), text clustering [[30]](https://paperpile.com/c/NPPxEM/NP5Q) and classification [[31]](https://paperpile.com/c/NPPxEM/73kP), recommender systems [[32]](https://paperpile.com/c/NPPxEM/1mjP), and anomaly detection [[33]](https://paperpile.com/c/NPPxEM/ZV6P). Text-embeddings can be generated by natural language processing models such as Word2Vec, GloVE, FastText or through large language models (LLM) such as BERT, GPT, ELMO [[27]](https://paperpile.com/c/NPPxEM/bKvK). In this paper, we generated text-embeddings from the following two embedding models offered by Open AI: text-embedding-ada-002 (referred as ADA002 in rest of the text) and text-embedding-3-large (referred as LTE-3 in rest of the text) [[34]](https://paperpile.com/c/NPPxEM/l3Uz). LTE-3 is a more recent and improved model and generates embeddings that have 3072 dimensions, whereas ADA002 generates embeddings consisting of 1536 dimensions.

We used both LTE-3 and ADA002 to generate embeddings for all the tumors identified in clinical trials, each term in every edition of the WHO database, and all the terms in the NCIT database which served as inputs to CANTOS. The first text-embedding based standardization method implemented by CANTOS involved calculating the respective Euclidean distances in the embedding space (LTE-3 or ADA002) between each tumor name identified in the CTR and every standardized tumor term in the WHO and NCIt database and then mapping the tumor name from CTR to the nearest standardized term. CANTOS ran this method using each set of embeddings(LTE-3 or ADA002) and standardized the tumor names in CTR with respect to the 5th edition of WHO database, all editions (3rd-5th) of the WHO database, and the NCIt database.

***Text Embedding Analysis: Embeddings and Clustering*** Similar to CANTOS's approach of using edit distances to compute divergence matrices for AP clustering for performing standardization on clusters, in this approach, CANTOS calculated the pairwise Euclidean distances in the embedding space (LTE-3 or ADA002) between tumor names in the CTR and terms from the WHO and NCIt databases. However, calculating the pairwise Euclidean distance in the embedding space is computationally expensive and time consuming, as the embedding space has a large number of dimensions for both ADA002 (1536 dimensions) and LTE-3 (3072 dimensions) embeddings. To address this issue, CANTOS applied principal component analysis (PCA) to each set of embeddings (ADA002 and LTE-3) and based on the iteration of pipeline that depended on the edition of WHO (5th Edition or All Editions) database used in the pipeline, generated four sets of PCA-transformed embeddings. The dimensions of the four PCA-transformed embedding spaces are summarized in Table 1. For each case, CANTOS retained the minimum number of principal components necessary to explain 80% of the variance in the data.

**Table 1: PCA dimensions for each embeddings based on WHO database editions**

| **Tumor Terms** | **Dimensions for PCA+ADA002** | **Dimensions for PCA+LTE-3** |
| --- | --- | --- |
| CT + NCIT + WHO 5th Edition | 136 | 178 |
| CT + NCIT + WHO All Edition | 141 | 185 |

With the four sets of PCA-transformed embeddings, CANTOS calculated the pairwise Euclidean distance that was used for AP clustering. Once AP clustering is completed, CANTOS performs cluster size analysis by computing the z-scores for each cluster based on the number of cluster members. The default threshold for large clusters in CANTOS is a z-score of 2.5, i.e. any clusters with a z-score greater than 2.5 were designated as large clusters. Using the z-score threshold of 2.5, CANTOS was able to determine the maximum number of members per cluster. For each cluster that had a z-score greater than 2.5, CANTOS performed AP within these clusters until either their sizes were below or equal to the maximum number of cluster members or the AP clustering algorithm converged. The use of z-score for determining large clusters differs from the edit distance-based AP clustering method in the previous section where the median cluster size was used as the threshold for determining the large clusters in CANTOS. This is because we observed that for embedding-based AP clustering, the median cluster size was lower than the maximum cluster size established by z-score based clustering. Due to this several clusters which had fairly homogeneous cluster members were determined to be large and required further nested clustering. The maximum cluster size determined using z-score was larger and determined fewer such clusters to be large, thus we selected it to be the threshold for determining large clusters in CANTOS. It should be noted that CTR has a diverse range of tumor names, and thus clustering these tumor names will produce clusters of non uniform cluster size, hence it is not trivial to estimate a maximum cluster size when we consider the variation in the entire dataset. With more curation and classification of the tumors within the CTR, one can get a more accurate estimate of a reasonable cluster size for each tumor type.

After the clustering was completed, CANTOS performed isolation forest and LOF analysis to determine outliers within each cluster just as it did in the case for edit-distance based AP clustering. The hyperparameters for both isolation forest and LOF analysis were kept the same as they were for edit-distance based AP clustering. Following the outlier detection step, CANTOS iterate through each cluster and determines the standardized term from the WHO (5th Edition and All Edition) and the NCIt databases that is closest to each cluster member by computing the Euclidean distance in the embedding space (not the PCA-transformed space).

If a majority of the tumor names in a cluster are close to a specific standardized term, then all the tumor names are mapped to that standardized term. In case there is a tie, where two or more standardized terms are equally represented in a cluster, then each tumor name within that cluster is assigned to its closest matching standardized tumor name. The final standardization process is similar to the standardization process discussed in the edit-distance based AP clustering, however, instead of edit distances, we used the Euclidean distance in the embedding space to determine the closest standardized terms. In Table 2, we compare the number of AP clusters when we use text-embeddings and text-matching (edit distances).

**Table 2: Number of clusters from AP clustering under embedding and text-matching based methods**.

| **Basis** | **Affinity Propagation Clustering Divergence Metric** | **Number of Clusters for CT Terms, NCIt Terms, All Editions WHO Terms** | **Number of Clusters for CT Terms, NCIt Terms, 5th Edition WHO** |
| --- | --- | --- | --- |
| Text Match | Cosine | 1040 | 967 |
| Text Match | Levenshtein | 2020 | 1808 |
| Text Match | Jarro Winkler | 1965 | 1785 |
| Embedding | ADA002 + Euclidean Dist | 3790 | 3456 |
| Embedding | LTE-3 + Euclidean Dist | 3894 | 3427 |

In addition to AP clustering, CANTOS also implemented K-means clustering on the PCA transformed embeddings to standardize the tumor names in CTR. Unlike AP clustering, the K-means algorithm requires the user to define the numbers of clusters to be formed, “K”, as a hyperparameter [[35]](https://paperpile.com/c/NPPxEM/wp0i). Since we do not have any a priori information on the types of tumors that are present in the CTR and have no means to classify the tumors based on their tissue or molecular subtypes, we needed to use computational methods to decide on a value for the number of clusters to provide as an input to the K-means algorithm. To determine the number of clusters, we implemented a commonly used cluster performance metric known as the silhouette coefficient [[36]](https://paperpile.com/c/NPPxEM/rUdk) within CANTOS. After the clustering is completed, the silhouette coefficient is computed for each data point. A silhouette coefficient ranges from -1 to 1. A silhouette coefficient of 1 signifies that the data point is well-matched to other elements in its own cluster and poorly matched to members of neighboring clusters [[37]](https://paperpile.com/c/NPPxEM/HATf). A silhouette coefficient of 0 indicates that the data point is at the decision boundary of neighboring clusters and a score of -1 indicates that the data point is poorly matched with other cluster members and likely assigned to an incorrect cluster [[37]](https://paperpile.com/c/NPPxEM/HATf). Intuitively, a higher silhouette coefficient for a data point represents high cohesion of that data point with rest of the cluster members and high separation from members of neighboring clusters.

CANTOS iterates through several values of “K” and performs K-means clustering and calculates the silhouette coefficient for each data point. For each cluster, CANTOS calculates the average silhouette coefficient which indicates the performance for that cluster. CANTOS also computed the average of each of the averaged silhouette coefficients per cluster, this produces a metric that can be used to evaluate the overall clustering performance of the K-means algorithm for a given value of “K”. We refer to this metric as the mean silhouette score which ranges from [-1,1] and a higher positive value indicates better clustering performance. Using this method, CANTOS evaluated the mean silhouette score for various values of “K” under both ADA002 and LTE-3 embeddings for each iteration (WHO database 5th Edition and WHO database All Editions) . In Figure 3, we plot the mean silhouette score for each of these cases.

**Figure 3: Average Silhouette Score vs Number of clusters (K) used in K-means. a. ADA002 when all editions of the WHO database are used. b. ADA002 when 5th edition of WHO database are used c. LTE-3 when all editions of WHO database are used d. LTE-3 when 5th editions of WHO database are used**

Once the clustering is completed using K-means, CANTOS follows the exact same steps for outlier detection (isolation forest and LOF analysis) and standardization (compute euclidean distances with standardized term and identify the closest match) as it did for embedding base AP clustering, while maintaining the exact hyperparameter configurations. A detailed view of the text-embedding based standardization pipeline is displayed in supplemental figure SSSSSS and a brief summary is presented in figure 2.

**RESULTS**

In this paper, we designed and implemented a computational pipeline CANTOS to extract tumor names from the CTR and standardized their nomenclature in accordance with the WHO and NCIt databases. The pipeline extracted 13,230 tumors from the CTR and identified 6,324 of these tumors as pediatric. The pipeline implemented 12 methods to standardize the tumor terms from the CTR. These methods were based on text-matching algorithms (edit-distances) and text embedding. To evaluate the performance of each of these methods, we required the ground truth or the appropriate standardized tumor names for each of the 13,230 clinical trials tumors. Since this information is not available and manual annotation of all the tumors extracted from the CTR is not feasible, we arbitrarily sampled 1,600 tumor names from the 13,230 tumor names for ground truth annotation inorder to evaluate the performance of our methods.

For these 1,600 tumors, we annotated the ground truths with respect to only the 5th edition (latest) and all editions (3rd,4th, and 5th) of WHO database. We did not evaluate the performance on the NCIt tumor terms, as the WHO database is considered as the gold standard for tumor nomenclature. During the ground truth annotation process, we noticed that several CTR tumors either had multiple ground truths associated with them or did not have ground truths available from the WHO database. Tumors from the CTR that could not be manually assigned a ground truth from the WHO database were excluded when evaluating the accuracy of each method. When only the 5th edition of the WHO database was used for standardization, we identified 567 CTR tumors that did not have a ground truth. When we considered all editions of the WHO database, we identified 482 CTR tumors that did not have a ground truth. This is a consistent finding as all editions of the WHO database have a greater number of standardized tumor terms (compared to only the 5th edition, which contains only the currently accepted WHO terms but not all terms that may have been used in the past) to which the clinical trials tumors can be mapped. Therefore, out of the 1,600 terms chosen for ground truth annotation, we evaluated the accuracy for 1,033 terms when we considered only the 5th edition of the WHO database for standardization and 1,118 terms when we considered all editions of the WHO database. To compute the accuracy of each method, we simply count the instances in which a given method identified at least one ground truth associated with the tumor name drawn from the CTR and divide it by total number of terms (1033 for 5th Edition of WHO database or 1118 for All Editions of WHO database). We report the accuracy of each method for the all editions of WHO database in Table 3 and for WHO database 5th Edition in Table 4.

**Table 3: CANTOS Accuracies for Standardization Methods when all Editions of WHO terms are used**

| **Ranking** | **Basis** | **Methods** | **Accuracy All Editions WHO** |
| --- | --- | --- | --- |
| 1 | Embedding | LTE-3 + Euclidean Dist | 0.6851521 |
| 2 | Embedding | LTE-3 + AP | 0.6708408 |
| 3 | Embedding | ADA002 + Euclidean Dist | 0.6618962 |
| 4 | Embedding | ADA002 + AP | 0.6466905 |
| 5 | Embedding | LTE-3 + K-means | 0.6449016 |
| 6 | Embedding | ADA002 + K-means | 0.6359571 |
| 7 | Text Match | Levenshtein | 0.3246869 |
| 8 | Text Match | Levenshtein + AP | 0.2924866 |
| 9 | Text Match | Jarro Winkler | 0.2549195 |
| 10 | Text Match | Jarro Winkler + AP | 0.244186 |
| 11 | Text Match | Cosine | 0.2388193 |
| 12 | Text Match | Cosine + AP | 0.2271914 |

**Table 4: CANTOS Accuracies for Standardization Methods when only 5th Editions of WHO terms are used**

| **Ranking** | **Basis** | **Methods** | **Accuracy 5th Edition WHO** |
| --- | --- | --- | --- |
| 1 | Embedding | LTE-3 + Euclidean Dist | 0.6563408 |
| 2 | Embedding | LTE-3 + AP | 0.6456922 |
| 3 | Embedding | LTE-3 + K-means | 0.6360116 |
| 4 | Embedding | ADA002 + Euclidean Dist | 0.6292352 |
| 5 | Embedding | ADA002 + AP | 0.6263311 |
| 6 | Embedding | ADA002 + K-means | 0.6050339 |
| 7 | Text Match | Levenshtein | 0.3059051 |
| 8 | Text Match | Levenshtein + AP | 0.286544 |
| 9 | Text Match | Jarro Winkler | 0.2342691 |
| 10 | Text Match | Jarro Winkler + AP | 0.232333 |
| 11 | Text Match | Cosine + AP | 0.2197483 |
| 12 | Text Match | Cosine | 0.2178122 |

Table 3 and Table 4 show that text-embedding-based methods outperform text-match-based methods irrespective of which variation of the WHO database was used for standardization. Typically, methods utilizing LTE-3 embeddings performed better than ADA002 embeddings, with method LTE-3+K-means as the exception, which performed marginally worse than ADA002+AP and ADA002+Euclidean Dist when standardized against all editions of the WHO database (Table 3). However, it should be noted that LTE-3+K-means ranked higher than ADA002+K-means when standardized against either editions of the WHO database. We attribute the better performance of LTE-3-based methods to the fact that LTE-3 embeddings have twice the number of dimensions as ADA002 and are able to better capture the complexity in the input data.

Among the edit distances, Levenshtein distance performed better than Jarro-Winkler distance and cosine distance or any of their implementations involving AP clustering. The Jarro-Winkler distance is useful when there are minor discrepancies between the texts being compared and if there are common prefixes between the texts, whereas cosine distance is based on the frequency of occurrence of each word (“bag of words”) in a text and does not take into account the order of words. Comparatively, Levenshtein distance is a simpler algorithm and only counts the number of edit operations needed to transform one text to another, does not factor the prefix similarity, and maintains the order of words/alphabet and is likely why it performed better than methods based on the other two edit distances. The ground truth annotations of the 1,600 clinical trials tumors along with their standardization results are available in Supplementary File S8 (for WHO database All Editions) and Supplementary File S9 (for WHO database 5th Edition). For each iteration of the pipeline, we report the WHO and NCIT standardized terms for each tumor identified in the CTR in the following supplementary files: Supplementary File S10-S13.

**Discussion:**

The CTR contains information on tumors that can be integrated with other external databases to gain insights on the therapeutic and drug-target landscapes associated with each tumor. However, the raw tumor names from the CTR cannot be directly linked to other databases as they suffer from various forms of inconsistencies such as extraneous information, typographical errors, missing values, non-standard nomenclature, etc.Furthermore, the tumor names are automatically identifiable in the CTR, thus they need to be first extracted. Therefore, to use the tumor names from the CTR , there is a need to identify and standardize them. To this end, in this study, we developed CANTOS, a computational pipeline to extract tumor names from the CTR and standardize them according to the WHO (5th edition and all editions) and NCIt databases.

CANTOS classified the identified tumor names from the CTR as adult or pediatric, and we manually validated the classification of each tumor. For pediatric tumors, we further assigned citations confirming the classification (Supplementary File S5). Overall, CANTOS identified 13,230 unique tumor names from the CTR, of which 6,324 were pediatric. CANTOS standardized the extracted tumor names in accordance with standardized nomenclature in the WHO and NCIt databases using 12 methods that were based on text-matching (edit distances) or text-embedding. Given that the WHO database is considered the gold standard for clinical tumor nomenclature, we limited the evaluation of our methods only against this database. To assess accuracy of each method, we randomly selected 1,600 tumor names out of the 13,230 tumor names standardized by CANTOS and manually annotated their ground truths with respect to the 5th edition of the WHO database alone and then with all editions (3rd, 4th, and 5th) of the WHO database. We observed that when we used all the editions of the WHO database, we were able to manually annotate (ground truth) more tumor names in the CTR because the 5th edition of the WHO database has fewer terms compared to all editions of the WHO database. In general, the text-embedding based methods were more accurate than text-matching based methods, which we attribute to the fact that text-matching techniques are based on edit-distances and can only evaluate syntactical differences between text, whereas text-embeddings are able to capture the semantic and contextual meaning of text and map similar texts close to each other in the embedding space.

We generated the text embeddings from OpenAI’s LLM:text-embedding-ada-002 (ADA002) and text-embedding-3-large (LTE-3). We observed that the LTE-3 based methods performed better than the ADA002 methods, with the exception of LTE-3+K-means, which slightly underperformed compared to ADA002+Euclidean Dist and ADA002+AP when standardized against all the editions of the WHO database. Irrespective of the variation of the WHO database that was considered in the pipeline, LTE-3+Euclidean Dist achieved the highest accuracy followed by LTE-3+AP. LTE-3+Euclidean Dist standardizes the clinical trials tumor by identifying and assigning the WHO database term that is closest in terms of Euclidean distance in the LTE-3 embedding space. Compared to the LTE-3+AP method, the LTE-3+Euclidean Dist is a simpler and faster technique that does not require additional steps such as clustering, cluster size analysis and outlier detection.

As more samples from the CTR are annotated with their respective ground truth, the performance accuracies of each method will merge towards their true accuracies.

While we expect the accuracy to change, it is clear from our ground truth annotation of the 1,600 CTR tumor names that the text-embedding based methods will very likely outperform the text-matching (edit distance) based methods. Expert annotation of the tumors in clinical trials is essential for accurate performance evaluation of these methods and is a limitation in our study. Furthermore, as the CTR is updated, new tumor names need to be detected and potentially standardized, which will require rerunning the pipeline and manually validating the results which can be time consuming and labor intensive. In addition to requiring expert annotation of ground truths, there is a computational cost associated with running the CANTOS pipeline, generating text-embeddings, and storing the data, which can become expensive in the long run. Another limiting factor in this study are the embeddings that were generated by OpenAI. If the OpenAI models are updated or discontinued, we will need to switch to other available LLMs that generate embeddings. Furthermore, the LLMs that generate the embeddings for OpenAI are not specifically trained on a medical or tumor corpus, and an LLM which is trained on such a corpus will likely have better performance and will be able to differentiate between the tumors more precisely[(Stanford CRFM )](https://paperpile.com/c/NPPxEM/gCkD).

The CANTOS pipeline uses embeddings from large language models that may inadvertently produce outputs reflecting biases inherent in their training data. It is important to recognize that these outputs are not always neutral or free from error, and results should be interpreted with caution. Importantly, the CANTOS pipeline is designed solely for research analysis purposes and should not be applied in clinical or diagnostic settings. This tool is not intended for use in contexts where decisions may directly affect human health, treatment, or care. Any conclusions drawn from the use of CANTOS in research should be further reviewed and validated by clinical professionals and subjected to rigorous peer-reviewed testing before any potential medical or therapeutic applications.

The CANTOS pipeline provides a basis to extract and standardize the tumors from the CTR. While there are guidelines in place for submitting data to the CTR to maintain basic data integrity, there are no enforced protocols to standardize tumor names that are entered as conditions file in the CTR. While studies have called for standardization of clinical trials with respect to study design [[38,39]](https://paperpile.com/c/NPPxEM/9u0o+9AUN) evidence reproducibility [[40]](https://paperpile.com/c/NPPxEM/MrPy), there have been no studies to our knowledge that have attempted to standardize tumors or any other diseases in the CTR. Standardizing the tumor names in the CTR will make these tumor names searchable in other biomedical databases, which will allow researchers to quickly develop an expansive overview of the associated targets, drugs, and clinical outcomes for a given tumor.

**Conclusion:**

The CTR records information on various aspects of a clinical trial which includes the conditions being studied. The information is disseminated to the public in text file format. However, the CTR lacks neither provides a mechanism to identify tumor names from other conditions nor are the tumor names standardized according to the WHO or NCIt databases, making it challenging to extract and integrate these tumor names with other biomedical databases for downstream analysis. In this paper, we designed CANTOS, a computational pipeline to identify tumor names from the CTR and annotated them as adult or pediatric tumors. Furthermore, CANTOS implemented 12 methods to standardize the identified tumor names using text-matching and text-embedding based methods. We observed that embedding based methods performed better than text-matching methods, and in particular the LTE-3+Euclidean Dist method had the highest accuracy in standardizing the tumor names in the CTR. We standardize all the 13,230 tumors in the CTR with respect to both the WHO and NCIT database using all the methods and report them in our results.

**Author Contribution:**

**Supplementary Material:**

**Funding:**

**Conflict of Interest:**

**Data availability:**

**References**

1 [Bray F, Laversanne M, Sung H, *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229–63.](http://paperpile.com/b/NPPxEM/Weij)

2 [Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74:12–49.](http://paperpile.com/b/NPPxEM/6kRx)

3 [Matt GY, Sioson E, Shelton K, *et al.* St. Jude Survivorship Portal: Sharing and Analyzing Large Clinical and Genomic Datasets from Pediatric Cancer Survivors. *Cancer Discov*. 2024;14:1403–17.](http://paperpile.com/b/NPPxEM/tUKD)

4 [Aristizabal P, Winestone LE, Umaretiya P, *et al.* Disparities in Pediatric Oncology: The 21st Century Opportunity to Improve Outcomes for Children and Adolescents With Cancer. *Am Soc Clin Oncol Educ Book*. 2021;41:e315–26.](http://paperpile.com/b/NPPxEM/FRbF)

5 [Hunger Stephen P., Mullighan Charles G. Acute Lymphoblastic Leukemia in Children. *N Engl J Med*. ;373:1541–52.](http://paperpile.com/b/NPPxEM/68hp)

6 [Laetsch TW, DuBois SG, Bender JG, *et al.* Opportunities and Challenges in Drug Development for Pediatric Cancers. *Cancer Discov*. 2021;11:545–59.](http://paperpile.com/b/NPPxEM/NRZI)

7 [Renfro LA, Ji L, Piao J, *et al.* Trial Design Challenges and Approaches for Precision Oncology in Rare Tumors: Experiences of the Children’s Oncology Group. *JCO Precis Oncol*. 2019;3. doi:](http://paperpile.com/b/NPPxEM/Lq9U) [10.1200/PO.19.00060](http://dx.doi.org/10.1200/PO.19.00060)

8 [Rivers Z, Hyde B, Ronski K, *et al.* Exploring Barriers to Pediatric Cancer Clinical Trials: The Role of a Networked, Just-in-Time Study Program. *Clin Ther*. 2023;45:1148–50.](http://paperpile.com/b/NPPxEM/5cZt)

9 [National Institutes of Health Clinical Trials Registry. ClinicalTrials.gov.](http://paperpile.com/b/NPPxEM/hYaH) <https://clinicaltrials.gov/> [(accessed 26 August 2024)](http://paperpile.com/b/NPPxEM/hYaH)

10 [Zarin DA, Tse T, Williams RJ, *et al.* The ClinicalTrials.gov Results Database — Update and Key Issues. *N Engl J Med*. 2011;364:852–60.](http://paperpile.com/b/NPPxEM/Hrsy)

11 [Snášel V, Keprt A, Abraham A, *et al.* Approximate String Matching by Fuzzy Automata. *Man-Machine Interactions*. Springer Berlin Heidelberg 2009:281–90.](http://paperpile.com/b/NPPxEM/rIfO)

12 [van der Loo M. Stringdist: Approximate string matching, fuzzy text search, and string distance functions. CRAN: Contributed Packages. 2013.](http://paperpile.com/b/NPPxEM/MKyW)

13 [R Core Team (2024). *R: A Language and Environment for Statistical Computing*. *R Foundation for Statistical Computing,* Vienna, Austria.](http://paperpile.com/b/NPPxEM/hon3) [https://www.R-project.org/](https://www.r-project.org/)

14 [Frey BJ, Dueck D. Clustering by passing messages between data points. *Science*. 2007;315:972–6.](http://paperpile.com/b/NPPxEM/OxXw)

15 [Kitahara YFGI. Fast Algorithm for Affinity Propagation. In: Walsh T, ed. *Twenty-Second International Joint Conference on Artificial Intelligence*. IJCAI/AAAI :2238–43.](http://paperpile.com/b/NPPxEM/ZrGQ)

16 [Shi XH, Guan RC, Wang LP, *et al.* An incremental affinity propagation algorithm and its applications for text clustering. *2009 International Joint Conference on Neural Networks*. IEEE 2009.](http://paperpile.com/b/NPPxEM/vxqy)

17 [Shailendra Kumar Shrivastava, J.L.Rana, R.C.Jain. Text document clustering based on phrase similarity using affinity propagation. *International Journal of Computer Applications*. 2013;61. doi:](http://paperpile.com/b/NPPxEM/FX6U) [10.5120/10032-5077](http://dx.doi.org/10.5120/10032-5077)

18 [Cortes D. isotree: Isolation-Based Outlier Detection. CRAN: Contributed Packages. 2019.](http://paperpile.com/b/NPPxEM/5rKu)

19 [Liu FT, Ting KM, Zhou Z-H. Isolation Forest. *2008 Eighth IEEE International Conference on Data Mining*. IEEE 2008:413–22.](http://paperpile.com/b/NPPxEM/vpqB)

20 [Hahsler M, Piekenbrock M. Dbscan: Density-based spatial clustering of applications with noise (DBSCAN) and related algorithms. CRAN: Contributed Packages. 2015.](http://paperpile.com/b/NPPxEM/ibnD)

21 [Alghushairy O, Alsini R, Soule T, *et al.* A review of Local Outlier Factor algorithms for outlier detection in big data streams. *Big Data Cogn Comput*. 2020;5:1.](http://paperpile.com/b/NPPxEM/Yd50)

22 [Ding H, Ding K, Zhang J, *et al.* Local outlier factor-based fault detection and evaluation of photovoltaic system. *Solar Energy*. 2018;164:139–48.](http://paperpile.com/b/NPPxEM/tkjs)

23 [Xu H, Zhang L, Li P, *et al.* Outlier detection algorithm based on k-nearest neighbors-local outlier factor. *J Algorithm Comput Technol*. 2022;16. doi:](http://paperpile.com/b/NPPxEM/YhfR) [10.1177/17483026221078111](http://dx.doi.org/10.1177/17483026221078111)

24 [Morris J, Kuleshov V, Shmatikov V, *et al.* Text embeddings reveal (almost) as much as text. *Proceedings of the 2023 Conference on Empirical Methods in Natural Language Processing*. Stroudsburg, PA, USA: Association for Computational Linguistics 2023.](http://paperpile.com/b/NPPxEM/SePY)

25 [Mikolov T. Efficient estimation of word representations in vector space. *arXiv preprint arXiv:13013781*. Published Online First: 2013.](http://paperpile.com/b/NPPxEM/AIyW)

26 [Incitti F, Urli F, Snidaro L. Beyond word embeddings: A survey. *Inf Fusion*. 2023;89:418–36.](http://paperpile.com/b/NPPxEM/WbHn)

27 [Khattak FK, Jeblee S, Pou-Prom C, *et al.* A survey of word embeddings for clinical text. *J Biomed Inform*. 2019;100S:100057.](http://paperpile.com/b/NPPxEM/bKvK)

28 [Gökçe O, Prada J, Nikolov NI, *et al.* Embedding-based scientific literature discovery in a text editor application. *Proceedings of the 58th Annual Meeting of the Association for Computational Linguistics: System Demonstrations*. Stroudsburg, PA, USA: Association for Computational Linguistics 2020.](http://paperpile.com/b/NPPxEM/fu7E)

29 [Mai G, Janowicz K, Yan B. Combining text embedding and knowledge graph embedding techniques for academic search engines. In: Key-Sun Choi, Luis Espinosa Anke, Thierry Declerck, Dagmar Gromann, Jin-Dong Kim, Axel-Cyrille Ngonga Ngomo, Muhammad Saleem, Ricardo Usbeck, ed. *Joint proceedings of the 4th Workshop on Semantic Deep Learning (SemDeep-4) and NLIWoD4: Natural Language Interfaces for the Web of Data (NLIWOD-4) and 9th Question Answering over Linked Data challenge (QALD-9) co-located with 17th International Semantic Web Conference (ISWC 2018)*. CEUR 2018:77–88.](http://paperpile.com/b/NPPxEM/8uDZ)

30 [Mehta V, Bawa S, Singh J. WEClustering: word embeddings based text clustering technique for large datasets. *Complex Intell Systems*. 2021;7:3211–24.](http://paperpile.com/b/NPPxEM/NP5Q)

31 [Stein RA, Jaques PA, Valiati JF. An analysis of hierarchical text classification using word embeddings. *Inf Sci* . 2019;471:216–32.](http://paperpile.com/b/NPPxEM/73kP)

32 [Musto C, Semeraro G, de Gemmis M, *et al.* Learning word embeddings from Wikipedia for content-based recommender systems. *Lecture Notes in Computer Science*. Cham: Springer International Publishing 2016:729–34.](http://paperpile.com/b/NPPxEM/1mjP)

33 [Pande A, Ahuja V. WEAC: Word embeddings for anomaly classification from event logs. *2017 IEEE International Conference on Big Data (Big Data)*. IEEE 2017:1095–100.](http://paperpile.com/b/NPPxEM/ZV6P)

34 [New embedding models and API updates.](http://paperpile.com/b/NPPxEM/l3Uz) <https://openai.com/index/new-embedding-models-and-api-updates/> [(accessed 4 September 2024)](http://paperpile.com/b/NPPxEM/l3Uz)

35 [Wu J. Cluster Analysis and K-means Clustering: An Introduction. In: Wu J, ed. *Advances in K-means Clustering: A Data Mining Thinking*. Berlin, Heidelberg: Springer Berlin Heidelberg 2012:1–16.](http://paperpile.com/b/NPPxEM/wp0i)

36 [Shahapure KR, Nicholas C. Cluster Quality Analysis Using Silhouette Score. *2020 IEEE 7th International Conference on Data Science and Advanced Analytics (DSAA)*. IEEE 2020:747–8.](http://paperpile.com/b/NPPxEM/rUdk)

37 [Shutaywi M, Kachouie NN. Silhouette Analysis for Performance Evaluation in Machine Learning with Applications to Clustering. *Entropy* . 2021;23. doi:](http://paperpile.com/b/NPPxEM/HATf) [10.3390/e23060759](http://dx.doi.org/10.3390/e23060759)

38 [Canonica GW, Baena-Cagnani CE, Bousquet J, *et al.* Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy*. 2007;62:317–24.](http://paperpile.com/b/NPPxEM/9u0o)

39 [Katz MHG, Marsh R, Herman JM, *et al.* Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol*. 2013;20:2787–95.](http://paperpile.com/b/NPPxEM/9AUN)

40 [Dickersin K, Mayo-Wilson E. Standards for design and measurement would make clinical research reproducible and usable. *Proc Natl Acad Sci U S A*. 2018;115:2590–4.](http://paperpile.com/b/NPPxEM/MrPy)

**FIGURES**

**Figure 1**: **Tumor extraction and annotation pipeline**

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**Fig 2: Text match and text embedding pipeline summary.**

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**Figure 3: Average Silhouette Score vs Number of clusters (K) used in K-means. a. ADA002 when all editions of WHO terms are used. b. ADA002 when 5th edition of WHO terms are used c. LTE-3 when all editions of WHO terms are used d. LTE-3 when 5th editions of WHO terms are used**

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**Supplemental Figure SSSSS: Text Match Pipeline using Edit Distances**

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**Supplemental Figure SSSSS: Text Match Pipeline using ADA002 and LTE-3 Embeddings**

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**SUPPLEMENTARY DATA:**

**Table S1: Conditions data with MeSH Terms:** This table was created by performing a full join on the files “conditions.txt” and “browse\_conditions.txt”, the files were joined on clinical trials ID.

| NCT ID | Condition name | MeSH term |
| --- | --- | --- |
| NCT05082610 | triple negative breast cancer | neoplasms,triple negative breast neoplasms,carcinoma, non-small-cell lung,breast neoplasms,neoplasms by site,breast diseases,skin diseases,carcinoma, bronchogenic,bronchial neoplasms,lung neoplasms,respiratory tract neoplasms,thoracic neoplasms,lung diseases,respiratory tract diseases |
| NCT04254107 | triple negative breast cancer | lymphoma,carcinoma,lymphoma, t-cell, peripheral,lymphoma, large b-cell, diffuse,triple negative breast neoplasms,squamous cell carcinoma of head and neck,stomach neoplasms,neoplasms by histologic type,neoplasms,lymphoproliferative disorders,lymphatic diseases,immunoproliferative disorders,immune system diseases,neoplasms, glandular and epithelial,neoplasms by site,carcinoma, squamous cell,lymphoma, b-cell,lymphoma, non-hodgkin,lymphoma, t-cell,breast neoplasms,breast diseases,skin diseases,head and neck neoplasms,gastrointestinal neoplasms,digestive system neoplasms,digestive system diseases,gastrointestinal diseases,stomach diseases |
| NCT01590680 | neuroblastoma | neuroblastoma,pheochromocytoma,paraganglioma,neuroectodermal tumors, primitive, peripheral,neuroectodermal tumors, primitive,neoplasms, neuroepithelial,neuroectodermal tumors,neoplasms, germ cell and embryonal,neoplasms by histologic type,neoplasms,neoplasms, glandular and epithelial,neoplasms, nerve tissue,neuroendocrine tumors |
| NCT04081701 | medulloblastoma | adenoma,meningioma,medulloblastoma,paraganglioma,pituitary neoplasms,esthesioneuroblastoma, olfactory,central nervous system neoplasms,hemangioblastoma,neoplasms, glandular and epithelial,neoplasms by histologic type,neoplasms,pituitary diseases,hypothalamic diseases,brain diseases,central nervous system diseases,nervous system diseases,endocrine system diseases,neoplasms, nerve tissue,neoplasms, vascular tissue,meningeal neoplasms,nervous system neoplasms,neoplasms by site,glioma,neoplasms, neuroepithelial,neuroectodermal tumors,neoplasms, germ cell and embryonal,neuroectodermal tumors, primitive,neuroendocrine tumors,endocrine gland neoplasms,hypothalamic neoplasms,supratentorial neoplasms,brain neoplasms,neuroblastoma,neuroectodermal tumors, primitive, peripheral,olfactory nerve diseases,cranial nerve diseases,hemangioma, capillary,hemangioma |
| NCT04294784 | gastroesophageal cancer | NA |
| NCT02669914 | gastroesophageal cancer | lung neoplasms,carcinoma, non-small-cell lung,colorectal neoplasms,pancreatic neoplasms,ovarian neoplasms,brain neoplasms,kidney neoplasms,carcinoma, renal cell,breast neoplasms,respiratory tract neoplasms,thoracic neoplasms,neoplasms by site,neoplasms,lung diseases,respiratory tract diseases,carcinoma, bronchogenic,bronchial neoplasms,intestinal neoplasms,gastrointestinal neoplasms,digestive system neoplasms,digestive system diseases,gastrointestinal diseases,colonic diseases,intestinal diseases,rectal diseases,endocrine gland neoplasms,pancreatic diseases,endocrine system diseases,ovarian diseases,adnexal diseases,genital diseases, female,female urogenital diseases,female urogenital diseases and pregnancy complications,urogenital diseases,genital neoplasms, female,urogenital neoplasms,genital diseases,gonadal disorders,central nervous system neoplasms,nervous system neoplasms,brain diseases,central nervous system diseases,nervous system diseases,urologic neoplasms,kidney diseases,urologic diseases,male urogenital diseases,adenocarcinoma,carcinoma,neoplasms, glandular and epithelial,neoplasms by histologic type,breast diseases,skin diseases |

It must be noted that the CTR recommends adding relevant Medical Subject Headings (MeSH) terms or terms from another controlled vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that have been mapped to MeSH within the Unified Medical Language System (UMLS) metathesaurus for each of the conditions. While this recommendation adds a level of standardization to the disease/condition names present in the CTR, the MeSH terms by themselves often fall short of describing the disease or condition accurately. Furthermore, for a given disease/condition there may be multiple associated MeSH terms, thereby leaving it to the user of the data to establish the most appropriate MeSH term for that disease/condition. Additionally, for certain records in the CTR, there might be no associated MeSH terms provided for a disease/condition name, therefore solely using the MeSH terms for analyzing the diseases or conditions that are the subject of a clinical trial record is not reliable. Therefore it is evident that the MeSH terms cannot be used to replace the terms enlisted in the conditions file, as the MeSH terms fail to accurately capture the specific information being conveyed by the conditions. In Supplementary Table S1, we provide examples of clinical trial records with their disease/condition names and associated mesh terms to illustrate the incompatibilities between condition names and MeSH terms.

For example, in Supplementary Table S1, the condition “triple negative breast cancer” is

associated with two clinical trial studies with the identifiers (NCT IDs) NCT05082610 and NCT04254107. Each of these studies lists the various MeSH terms associated with “triple negative breast cancer” with the most appropriate MeSH term being “triple negative breast neoplasms”. However, there are other associated MeSH terms for each of these studies which are not appropriate: for study NCT05082610 there are MeSH terms such as “carcinoma, non-small-cell lung” and “respiratory tract diseases” while study NCT04254107 has associated MeSH terms such as “lymphoma” and “stomach neoplasms”, which do not describe the condition of “triple negative breast cancer”. Furthermore, the MeSH terms are not identical between studies where the condition names are the same, which adds to the inconsistencies between records with same condition names. For instance, NCT04254107 contains various MeSH terms associated with lymphomas such as “lymphoma, b-cell”, “large b-cell”, “lymphoma, large b-cell, diffuse”, “lymphoma, t-cell, peripheral”, etc., but these terms are not contained in the list of MeSH terms for NCT05082610. We can also see in study NCT04294784, for the condition “gastroesophageal cancer”, there are no MeSH terms, but for the same condition with a different NCT ID (NCT02669914), there are multiple associated MeSH terms. We conclude from our analysis that the MeSH terms–even though they are internally standardized– are not suitable to be used to identify the exact term and condition name for the conditions they encode. Therefore, even though we observed that the condition names from the CTR contained syntactic and semantic inconsistencies, we decided to use the terms from the conditions file to extract tumor names and map them to their standardized nomenclature in the WHO Classification of Tumors system (referred to as the “WHO database” in the rest of the paper) (<https://tumourclassification.iarc.who.int/welcome/>) or National Cancer Institute Thesaurus (“NCIt database”) (<https://ncithesaurus.nci.nih.gov/ncitbrowser/>).

**S2: data\_download\_instructions.docx**

**Table S3: Types of interventions listed in interventions file in the CTR**

| **Index** | **Type of intervention** | **Included in analysis** |
| --- | --- | --- |
| 1 | Drug | Yes |
| 2 | Biological | Yes |
| 3 | Radiation | No |
| 4 | Device | No |
| 5 | Behavioral | No |
| 6 | Other | No |
| 7 | Genetic | Yes |
| 8 | Procedure | No |
| 9 | Combination Product | Yes |
| 10 | Dietary Supplement | No |
| 11 | Diagnostic Test | No |

**Table S4: contains the key words used for detecting tumors**

| # | Tumor Key Words |
| --- | --- |
| 1 | cancer |
| 2 | carcinoma |
| 3 | adenocarcinoma |
| 4 | tumor |
| 5 | lymphoma |
| 6 | blast |
| 7 | myeloma |
| 8 | melanoma |
| 9 | leukemia |
| 10 | astrocytoma |
| 11 | malignant |
| 12 | neoplasm |
| 13 | neoplasia |
| 14 | mesothelioma |
| 15 | ependymoma |
| 16 | glioma |
| 17 | thymoma |
| 18 | waldenstrom macroglobulinemia |
| 19 | myelodysplastic syndrome |
| 20 | polycythemia vera |
| 21 | myelofibrosis |
| 22 | myeloproliferative |
| 23 | sarcoma |
| 24 | gist-plus syndrome |
| 25 | macroglobulinemia |
| 26 | mycosis fungoides |
| 27 | sezary's disease |
| 28 | plasmacytoma |

**S5:** tumor\_annotated\_adult\_ped.csv

**Supplementary Table S6: Discrepancies associated with Conditions Data**

| **NCT ID** | **Disease Name** | **Issue** | **Standardized WHO Tumor Name** |
| --- | --- | --- | --- |
| NCT02172768 | acute myeloid leucaemia | Leukemia is not spelled correctly. | acute myeloid leukaemia |
| NCT02658838 | lovastatin/ticagrelor [va drug interaction] | Drug names are presented instead of diseases. | Does not exist |
| NCT01291602 | healthy male and female japanese volunteers | Description of study participant is provided instead of diseases. | Does not exist |
| NCT04323956 | ann arbor stage iii follicular lymphoma | Extra information provided on staging of the tumor. | follicular lymphoma |
| NCT02637531 | adrenocortical carcinoma (part g) | Extra information presented inside parenthesis. | adrenal cortical carcinoma |
| NCT03712605 | pathologic stage i merkel cell carcinoma ajcc v8 | Extra information on staging of the tumor. | merkel cell carcinoma |
| NCT01780740 | disorder; heart, functional, postoperative, cardiac surgery | Multiple clinical terms entered in a comma separated format. | Does not exist |
| NCT01963481 | metastatic beast cancer | Breast cancer is spelled incorrectly. | invasive breast carcinoma of no special type (5th Edition WHO) ,  invasive breast carcinoma (3rd Edition WHO) |
| NCT01782235 | primary sj√∂gren's syndrome (pss) | Special characters present in disease name. | Does not exist |
| NCT01209195 | locally advanced/metastatic or recurrent ovarian cancer, fallopian tube cancer, | Multiple tumor names | Does not exist |
| NCT01863108 | tumor vaccines | Description of tumor intervention | Does not exist |
| NCT02018874 | solid tumors and non-hodgkin's lymphoma | Solid tumors is a vague term whereas non-Hodgkin’s lymphoma is specific and a childhood tumor. | Does not exist |
| NCT05050630 | at least one positive lesion according to the 2014 lugano criteria for hodgkin's and non-hodgkin's lymphoma | Vague tumor description. It is not clear whether the tumor is Hodkin’s or non-Hodgkin’s tumor. | Does not exist |

**S7: Demonstration of comparing strings using edit distances**

In order to illustrate the concept of how strings can be compared using edit distances, consider the following two strings

String 1: Breast Cancer

String 2: Brain Cancer

Let us now suppose, we can make the following operations: deletions, substitution, and insertion to transform string 1 to string 2. Then we can proceed to transform String 1 to String 2 in the following ways:  
  
Table A1: step by step demonstration of comparing strings using edit distances.

| Method 1 | Method 1 operation | Method 2 | Method 2 operation |
| --- | --- | --- | --- |
| Breast Cancer |  | Breast Cancer |  |
| Brast Cancer | Delete ‘e’ | Braast Cancer | Substitute ‘e’ with ‘a’ |
| Bras Cancer | Delete ‘t’ | Braist Cancer | Substitute ‘a’ with ‘i’ |
| Bra Cancer | Delete ‘s’ | Braint Cancer | Substitute ‘s’ with ‘n’ |
| Brai Cancer | Insert ‘i’ | Brain Cancer | Delete ‘t’ |
| Brain Cancer | Insert ‘n’ |  |  |

We can observe from Table A1 that the two methods transform string 1 to string 2, but method 2 employs fewer steps to achieve this objective. Furthermore, with the given set of operations the minimum number of steps required to transform string 1 to string 2 is four. This is achieved by method 2 , thus the edit distance between string 1 and string 2 is four. The set of operations that were used to transform the strings and method with which we calculated the edit distance is also known as the Levenshtein distance.

**S8:** tumor\_sample\_df\_gt\_annotated\_all\_sep11.csv

**S9:**tumor\_sample\_df\_gt\_annotated\_5th\_sep11.csv

**S10:** WHO\_Results\_all\_10sep.csv

**S11:** WHO\_Results\_5thed\_9sep.csv

**S12:** NCIT\_Results\_all\_10sep.csv

**S13:**NCIT\_Results\_5thed\_9sep.csv