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REVIEW ARTICLE

Data Analysis and Mapping of Research Interest in Clinical Trials of Tuberculosis by Text Mining Platform of Artificial Intelligence using Open-Source Tool Orange Canvas

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Abstract: *Background*: Reading every clinical trial for any disease is tedious, as is determining the current progress, especially when the number of clinical trials is huge. The Text Mining Platform of Artificial Intelligence (AI) can help to simplify the task.

***Methods*:** A large pool of tuberculosis clinical trials has been searched through the International Clinical Trial Registry Platform (ICTRP) and used as a textual dataset. The exported dataset of 1635 clinical studies, in a comma-separated format, is preprocessed for data analysis and text mining. Data preparation, corpus generation, text preprocessing, and finally, cluster analysis were carried out using the text-mining widget of the open-source machine learning tool. The hierarchical cluster analysis was used for mapping research interests in tuberculosis clinical trials.

***Conclusion*:** The data mining of the exported dataset of tuberculosis clinical trials uncovered interesting facts in terms of numbers. Text mining presented a total of 41 hierarchical clusters that were further mapped in twenty-five (25) different research interests among tuberculosis clinical trials. A novel technique for the rapid and practical review of major clinical trials is demonstrated. As an open-source and GUI-based tool is used for work, any researcher with working knowledge of text mining may also use this technique for other clinical trials.

Keywords: Text mining, data analysis, hierarchical cluster analysis, tuberculosis, clinical trials, ICTRP, AI.

1. INTRODUCTION

Tuberculosis is an ancient illness that claims millions of lives each year [1, 2]. Despite massive attempts to find the panacea, the numbers worsen. Tuberculosis with multidrug resistance (MDR) is now another problem for scientists [3-6]. Several clinical trials are registered around the globe, as well as myriads of research publications. The areas that have been explored so far need to be identified. Without this analysis, the study work cannot be directed in the right direction. This dataset is too big and continuously rising as well. Consequently, the present state of work in tuberculosis is difficult to grasp through the conventional way of literature review.

To increase the transparency in clinical trials and avoid biased or selective reporting of the results, many countries have adopted mandatory clinical trial registration prior to its execution. Furthermore, several journals have redefined their policies about the nonacceptance of research papers without the registration number for clinical trials. The WHO has also developed a shared database that gathers, compiles, and publishes meta-details of these registrations from various worldwide registries. Currently, the WHO's International Clinical Trial Registry Platform (ICTRP) has networked with 17 different country registries.

ICTRP enables registered clinical trials from many countries to be searched *via* the same web portal. This search platform does, however, have search and export facilities with limited filter options. Thus, one can export the entire list of the registered tuberculosis clinical trials, but it is difficult to understand the research trend between these lists without proper analysis. The ICTRP generated more than 1,600 results for a simple one-word query like "tuberculosis" (Portal was accessed in December 2019). This exported result includes fundamental pieces of clinical trial information such as Trial ID; Public Title, Scientific Title, Registration Date, Type of clinical trial, *etc*.

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The initial statistical analysis of such data is simple. However, the whole picture of clinical trials from the exported list of clinical trials needs to be understood for a strategic review. The abundance of clinical trials makes that task complex and time-consuming. Extracting scientific information from this massive pool of clinical trials by manually reading each one of them is cumbersome. This task can be simplified by stratification or clustering these clinical trials by their common research subjects or areas. Each such cluster represents a common area of research that is explored by that particular cluster's clinical trials.

Exported ICTRP results are mostly in text form and can be considered unstructured data. The text mining technique can help in analyzing and categorizing textual data from clinical trials [7-10]. Text mining is a technique employing natural language processing (NLP) to analyze texts from both supervised (structured) and unsupervised (unstructured) datasets. For example, those textual data are titles and abstracts of biomedical literature. The text mining technique transforms these texts into meaningful numbers that can be used to analyze and understand these enormous datasets further. Text mining can help categorize or cluster these clinical trials by their common area of research.

Methods for the text mining of biomedical literature [11-14] and patents [9, 15] are explored widely. However, not much is explored using the text mining technique for clinical trials. There are very few research works that have used either complicated processes or commercial software for clinical trial text mining [16]. The majority of end-users who use such clinical trial data for their research and health-related decisions are nonprogrammers. For the text mining of clinical trials, the graphical user interface (GUI)-based and the open-source tools need to be explored.

Orange (https://orange.biolab.si/) is an open-source tool for machine learning and data visualization [17-19]. This open-source tool is available for various operating systems like Windows, Linux, and Mac. A text mining widget of the Orange tool can be utilized for text mining and further analysis of exported results from ICTRP [20].

However, similar text mining and analysis can be performed for the results obtained from other databases. For example, the clinical trial registry of the USA (www.clinicaltrials.gov) can be utilized to search clinical trials of TB in the USA. Moreover, text mining can also be performed on it. Clinical Trial Registry of India (CTRI) is also rich in terms of data. It can be accessed from the website of CTRI (www.ctri.nic.in). However, they are not providing an export facility. Manual preparation of data in Microsoft Excel® is possible in the case of CTRI.

As shown in Fig. (**1**), text mining and analysis involve a few necessary steps, which include data retrieval, data preprocessing, gathering of textual data (corpus), preprocessing of text, and text mining at last.

In the present work, the text mining technique is employed using an open-source and GUI-based tool – Orange. Clinical trials on TB which are retrieved from ICTRP are utilized as unstructured textual data. Research interests and trends among registered TB clinical trials are mapped using the technique of text mining. Although the present work represents the data up to 2019, one can easily export the updated dataset and can perform text mining just by replacing older data. This method is reproducible and can be used in any other dataset of clinical trials. Besides the mapping of research interest, some interesting statistics and data mining of the retrieved clinical trials are also discussed in brief.

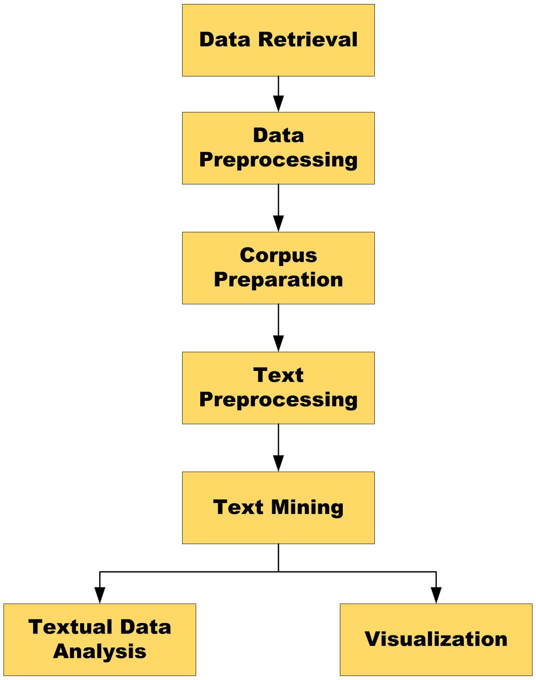


Fig. (1). Basic steps of text mining and analysis of textual data. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Compendiously is a novel approach for effortlessly reviewing the massive number of literature, which is explained lucidly in this article. Text mining is a known approach among data scientists. Nevertheless, it is almost impossible to apply for nonprogrammers. A simple and GUI-based method using the open-source tool is described here using the massive data of tuberculosis clinical trials as literature.

This article is ramified into three parts. The first part is a methodology, wherein a step-by-step process is explained, covering data collection, curation, text mining, and analysis. The second part is the result section. It depicts the outcome of text mining and analysis. It basically allows readers to understand how text mining revealed the numerous information from a large pool of tuberculosis's clinical trials. Lastly, the third part is the conclusion. It summarises information gathered from literature about tuberculosis. It also concludes the effectiveness and the easiness of the text-mining approach.

2. METHODOLOGY

2.1. Data Mining

Data Mining was performed over structured data of exported ICTRP results to understand the scenario of tuberculosis clinical trials across the globe. Various meta-analyses like country-wise and year-wise registration of clinical trials, distribution of gender among the registered clinical trials, availability of results, *etc*., were performed.

2.2. TEXT MINING

The method consists of five main steps, as shown in Fig. (**1**): (1) Data Retrieval; (2) Data Pre-Processing; (3) Corpus Preparation; (4) Text Pre-Processing; and finally (5) Text Mining. Microsoft Excel 2019, Orange version 3.24, Tableau 2019, Notepad, *etc*., are different tools that are used for different purposes. A computer system with the Intel Core i5-7200 CPU with 2.5 GHz speed and 64-bit Windows 10 operating system was used for the entire work. The system is equipped with 8 GB of RAM to ensure smooth system function.

2.2.1. Data Retrieval and Data Pre-processing

The IRCTP portal frequently updates its database. However, IRCTP's search portal was accessed in late December 2019. Therefore, the dataset will only cover clinical trials until 2019. A single keyword query was used with the word "Tuberculosis" to search the database. All result outputs were exported in the file format of comma-separated value (.csv) and renamed "core_data.csv." As shown in Table **1**, the forty fields were exported in the result. An example (regardless of any particular clinical trial) of each field is also shown in the table. This dataset covers a total of 1635 clinical trials of tuberculosis.

Necessary data refining was done manually, without any disruption to its scientific significance. For example, “male” and “males” both are manually corrected as “Male” in the field of gender. In the same way, “Intervention” and “Interventional” both are corrected as “Interventional” in the area of the study type. Microsoft Excel was utilized for this data preprocessing, and Tableau® Desktop (Trial Version) was utilized for data analysis and visualization.

2.2.2. Corpus Preparation

Each row of "core_data.csv" represents one individual clinical trial, as shown in Fig. (**2**). The text mining widget's "Import Document" tool in the Orange software can handle data only in text (.txt) file format. Therefore, an individual row (from core_data.csv) must be exported to the individual text file for the preparation of the corpus. This text file must be renamed with the respective clinical trial "Trial ID." The first row of the dataset, for example, is exported as a text file renamed as "ACTRN126100643077.txt."

For the text mining purpose, only “Public title” and “Scientific title” were exported into the text file, which embraces the scientific meaning of the clinical trial. Thus, each text file contains the titles of its respective clinical trial. A macro function of Microsoft Excel was used for the export of each row containing only public and scientific titles in a single text file and further renaming it with its "Trial ID." This execution has generated a total of 1635 text files, each containing the public and scientific title of their respective clinical trials.

As shown in Fig. (**3**), all text files, according to their source registry, were grouped into separate subfolders. These subfolders have been renamed according to their respective source registries. These sub-folders were renamed as per their respective source registry. The source registry ultimately represents an individual country where the particular clinical trial was registered. Therefore, a total of 15 subfolders with text files of their respective clinical trials were created in this way. As shown in Fig. (**3**), each sub-folder named after the source register represents their respective countries. All these sub-folders were stored in one principal folder named “Corpus”. This principal folder was used in the Orange software to create a corpus for further text mining.

This "Corpus" folder was browsed and selected using the Orange software's "Import Documents" tool. In Orange, each of the fifteen subfolders is referred like 15 different categories. The text files are grouped in subfolders and look like a structured dataset because they are marked with their respective "source registry." The textual dataset in those subfolders, however, is unstructured from the perspective of text mining. The entire dataset is available from the GitHub (https://github.com/Swayamprakashpatel/Tuberculosis_Clinical_Trial_TextMining.git)

Fig. (**4**) shows a basic workflow for text mining in the Orange software. The Import Documents tool is connected to the Corpus tool to generate a corpus. Corpus viewer, preprocess text, bag of words, distance, hierarchical clustering, distribution, and word cloud and data table widgets were connected in series as shown in the figure.

2.2.3. Text Pre-processing

Before the analysis, various text preprocessing was performed using the "Text Preprocessing" tool in the Orange.

Table **2** shows all of the options available in the "Text Preprocessing" tool. All words were transformed into lowercase, and if present, their accents were removed. By enabling the "parse Html" option, the HTML markups were removed from its text. URLs of the text data were simply disregarded. For the tokenisation, only the word and punctuation were taken into account. Words were lemmatized using "WordNet" as a lexical database instead of mere stemming. N-gram was set to a maximum of two (N=2) words.

Besides basic stop words and regular expressions in English, some other words had also been filtered from the text. These filter words are 'tuberculosis;' 'tb;' 'exclusion;' 'inclusion;' 'criteria;' 'treatment;' 'study;' 'patient;' 'therapy;' 'medicine;' 'effect;' 'clinical;' 'trial.' These are the most common words in any clinical trial and do not constitute the scientific sense or meaning of any clinical study (at least in this work). We recommend reading the tutorials provided by the Orange software over its website for a better understanding of this tool.

2.2.4. Text Mining

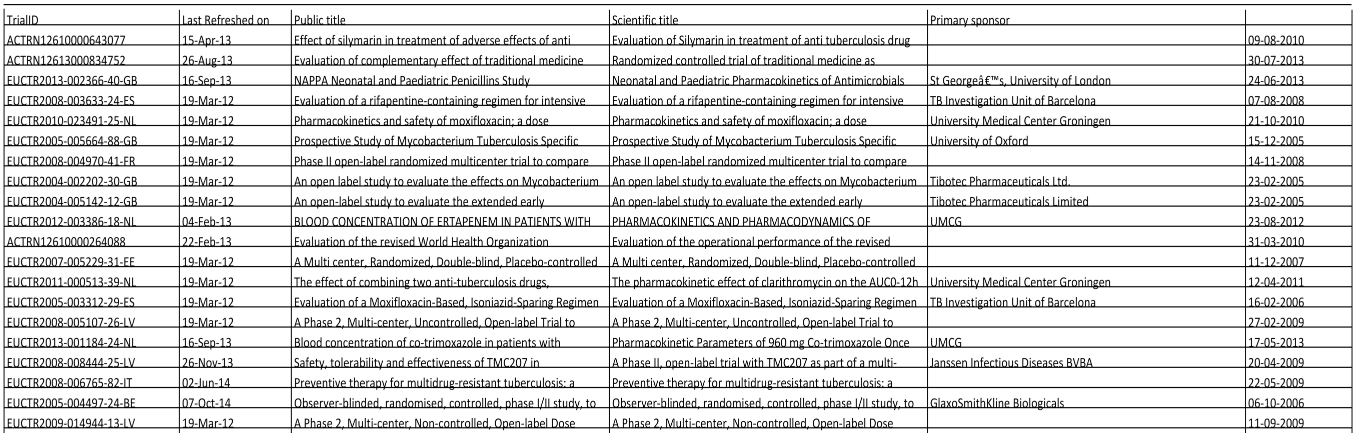
For text mining, a technique of cluster analysis was used to group the clinical trials with the common research interest. The hierarchical clustering (HC) technique was utilized to understand the various research interests among the registered clinical trials of tuberculosis. Hierarchical Cluster Analysis (HCA) uses an algorithm that keeps similar objects in common groups called clusters [21-24]. Depending upon

Table 1. Details of fields exported in the result from ICTRP.

No.	Field Title	Example
1.	Trial ID	ACTRN12610000643077
2.	Last Refreshed on	15-Apr-13
3.	Public title	Effect of silymarin in the treatment of adverse effects of anti-tuberculosis drugs.
4.	Scientific title	Evaluation of Silymarin in the treatment of anti-tuberculosis drug-induced hepatitis in patients newly diagnosed with tuberculosis.
5.	Acronym	ALTAC
6.	Primary sponsor	Government funding body National Institute of Tuberculosis and Lung Disease (NRITLD)
7.	Date registration	09/08/2010
8.	Date registration3	20100809
9.	Export date	12/26/2019 9:50:07 AM
10.	Source Register	ANZCTR
11.	Web address	http://www.anzctr.org.au/ACTRN12610000643077.aspx
12.	Recruitment Status	Recruiting
13.	Other records	No
14.	Inclusion age min	18 Years
15.	Inclusion age max	100 Years
16.	Inclusion of gender	Both males and females
17.	Date enrolment	01/10/2010
18.	Target size	60
19.	Study type	Interventional
20.	Study design	"Controlled: yes; Randomised: yes; Open: yes; Single-blind: no; Double-blind: no; Parallel group: yes; Cross over: no; Other: no; If controlled, specify comparator, Other Medicinal Product: yes; Placebo: no; Other: yes; Other specify the comparator: Rifampin, Pyrazinamide, Isoniazid"
21.	Phase	Phase 3
22.	Countries	Outside; Iran, the Islamic Republic Of
23.	Contact first name	Andre
24.	Contact last name	Dr. Majid Marjani
25.	Contact address	National Institute of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Dar Abad street, Niavaran, Tehran, post code:1955841452, Iran, Islamic Republic Of
26.	Contact email	marjani216@hotmail.com
27.	Contact tel	9.82126E+11
28.	Contact affiliation	Aarhus University Hospital
29.	Inclusion criteria	Inclusion criteria: New cases of tuberculosis
30.	Exclusion criteria	Exclusion criteria: 1. Infection with Human Immune deficiency virus 2. Infection with hepatitis B virus 3. Infection with hepatitis c virus 4. pregnancy 5. Breastfeeding
31.	Condition	Tuberculosis
32.	Intervention	Silymarin 420 mg per day, in three doses, it will start after diagnosis of drug-induced hepatitis and stop after normalization of liver function tests, as oral tablets

(Table 1) Contd….

No.	Field Title	Example
33.	Primary outcome	Normalization of liver function tests
34.	Results date posted	04/04/201
35.	Results date completed	31/10/2019
36.	Results URL link	https://clinicaltrials.gov/ct2/show/results/NCT00814671
37.	Retrospective flag	Yes
38.	Bridging flag true false	FALSE
39.	Bridged type	Parent
40.	Results yes no	yes



TrialID	Last Refreshed on	Public title	Scientific title	Primary sponsor	
ACTRN12610000643077	15-Apr-13	Effect of silymarin in treatment of adverse effects of anti	Evaluation of Silymarin in treatment of anti tuberculosis drug		09-08-2010
ACTRN12613000834752	26-Aug-13	Evaluation of complementary effect of traditional medicine	Randomized controlled trial of traditional medicine as		30-07-2013
EUCTR2013-002366-40-GB	16-Sep-13	NAPPA Neonatal and Paediatric Penicillins Study	Neonatal and Paediatric Pharmacokinetics of Antimicrobials	St Georgeâ€™s, University of London	24-06-2013
EUCTR2008-003633-24-ES	19-Mar-12	Evaluation of a rifapentine-containing regimen for intensive	Evaluation of a rifapentine-containing regimen for intensive	TB Investigation Unit of Barcelona	07-08-2008
EUCTR2010-023491-25-NL	19-Mar-12	Pharmacokinetics and safety of moxifloxacin; a dose	Pharmacokinetics and safety of moxifloxacin; a dose	University Medical Center Groningen	21-10-2010
EUCTR2005-005664-88-GB	19-Mar-12	Prospective Study of Mycobacterium Tuberculosis Specific	Prospective Study of Mycobacterium Tuberculosis Specific	University of Oxford	15-12-2005
EUCTR2008-004970-41-FR	19-Mar-12	Phase II open-label randomized multicenter trial to compare	Phase II open-label randomized multicenter trial to compare		14-11-2008
EUCTR2004-002202-30-GB	19-Mar-12	An open label study to evaluate the effects on Mycobacterium	An open label study to evaluate the effects on Mycobacterium	Tibotec Pharmaceuticals Ltd.	23-02-2005
EUCTR2004-005142-12-GB	19-Mar-12	An open-label study to evaluate the extended early	An open-label study to evaluate the extended early	Tibotec Pharmaceuticals Limited	23-02-2005
EUCTR2012-003386-18-NL	04-Feb-13	BLOOD CONCENTRATION OF ERTAPENEM IN PATIENTS WITH	PHARMACOKINETICS AND PHARMACODYNAMICS OF	UMCG	23-08-2012
ACTRN12610000264088	22-Feb-13	Evaluation of the revised World Health Organization	Evaluation of the operational performance of the revised		31-03-2010
EUCTR2007-005229-31-EE	19-Mar-12	A Multi center, Randomized, Double-blind, Placebo-controlled	A Multi center, Randomized, Double-blind, Placebo-controlled		11-12-2007
EUCTR2011-000513-39-NL	19-Mar-12	The effect of combining two anti-tuberculosis drugs,	The pharmacokinetic effect of clarithromycin on the AUC0-12h	University Medical Center Groningen	12-04-2011
EUCTR2005-003312-29-ES	19-Mar-12	Evaluation of a Moxifloxacin-Based, Isoniazid-Sparing Regimen	Evaluation of a Moxifloxacin-Based, Isoniazid-Sparing Regimen	TB Investigation Unit of Barcelona	16-02-2006
EUCTR2008-005107-26-LV	19-Mar-12	A Phase 2, Multi-center, Uncontrolled, Open-label Trial to	A Phase 2, Multi-center, Uncontrolled, Open-label Trial to		27-02-2009
EUCTR2013-001184-24-NL	16-Sep-13	Blood concentration of co-trimoxazole in patients with	Pharmacokinetic Parameters of 960 mg Co-trimoxazole Once	UMCG	17-05-2013
EUCTR2008-008444-25-LV	26-Nov-13	Safety, tolerability and effectiveness of TMC207 in	A Phase II, open-label trial with TMC207 as part of a multi-	Janssen Infectious Diseases BVBA	20-04-2009
EUCTR2008-006765-82-IT	02-Jun-14	Preventive therapy for multidrug-resistant tuberculosis: a	Preventive therapy for multidrug-resistant tuberculosis: a		22-05-2009
EUCTR2005-004497-24-BE	07-Oct-14	Observer-blinded, randomised, controlled, phase I/II study, to	Observer-blinded, randomised, controlled, phase I/II study, to	GlaxoSmithKline Biologicals	06-10-2006
EUCTR2009-014944-13-LV	19-Mar-12	A Phase 2, Multi-center, Non-controlled, Open-label Dose	A Phase 2, Multi-center, Non-controlled, Open-label Dose		11-09-2009

Fig. (2). Core data in comma-separated (.csv) file format (only the first few columns and rows shown here).

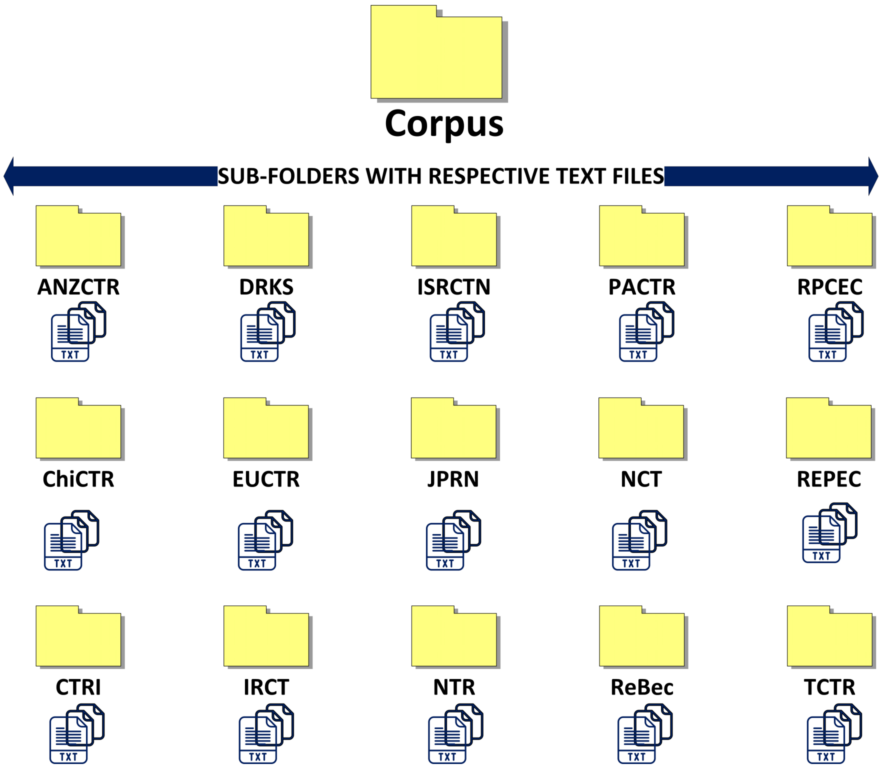


Fig. (3). Grouping of text files of the clinical trial as per respective source register in appropriate folders. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

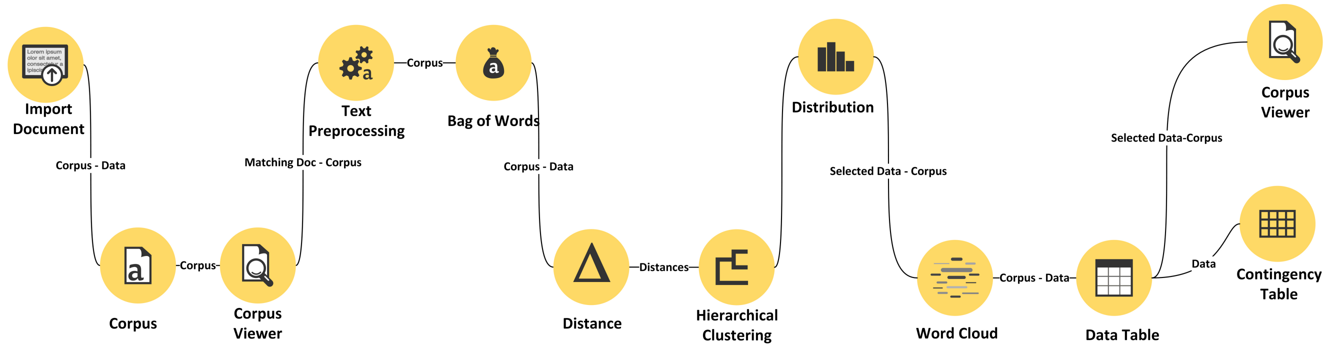


Fig. (4). Exemplary workflow of text mining in orange. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Text preprocessing.

Pre-processing Feature	Options	Status
Transformation	Lowercase	Enabled
	Remove Accents	Enabled
	Parse HTML	Enabled
	Remove URLs	Enabled
Tokenization	Word and Punctuation	Enabled
	Whitespace, Sentence, Regexp, Tweet	Disabled
Normalization	WordNet Lemmatizer	Enabled
	Porter stemmer, Snowball stemmer, UDPipe Lemmatizer	Disabled
Filtering	Stop word (English)	Enabled
	Stop word (Tuberculosis Word list.txt)	Enabled
	Regexp	Enabled
	Lexicon, Document Frequency, Most Frequent Token	Disabled
N-gram range	1-2	Enabled

the most occurring words, they are grouped in a common cluster. The top-down strategy has been used in this work to ensure effective clustering [25]. "Distance" and "Hierarchical clustering" are the widgets in the orange software which were used for the cluster analysis. Distance between the rows and a cosine distance matrix was utilized in the hierarchical clustering. Ward's method was chosen to cluster the clinical trials [26] effectively, and the dendrogram height ratio was set at 35 percent of the total height for the selection of clusters.

As shown in **Error! Reference source not found.**, the “hierarchical cluster” (HC) tool was connected to the “Distribution,” “Word Cloud,” “Data Table,” and “Contingency Table” tools in the series manner. “Selected Data-to-Data” and “Selected Data-to-Corpus” options were set as the connection between HC, distribution, and word cloud tools, respectively. At the same time, “corpus-to-data” and “data-to-data” connections were utilized for word cloud, data table, and contingency table tools. For the analysis of each cluster, the most common words were selected from the word cloud one by one until it covered all clinical trials in the contingency table. This list of words represents that particular cluster (Refer to Supplementary Table **1**). The meaningful research area was concluded manually from this list of words and considered as a common research interest of the clinical trials within the respective cluster.

In some clusters, the resolution of words for firm mapping of research interest is poor. We can not conclude a common research interest from their list of most frequent words. In such cases, it is imperative to perform subclustering. The process of sub-clustering is simple and similar to hierarchical clustering. It includes the selection of clusters from the distribution tool for which sub-clustering is required. Connect the distribution widget further to the new hierarchical clustering widget, followed by a new distribution widget and a new word cloud widget in series. Mapping of research interest can be further performed for the subclusters in a way similar to that performed for its parent cluster.

3. RESULTS AND DISCUSSION

3.1. Data Mining

As shown in Fig. (**5**), the United States has made significant contributions, among others, in terms of the number of clinical trials on tuberculosis. The Year-wise contribution (Fig. **6**) of clinical trials on tuberculosis also revealed a steady increase in the number of registrations in India and China. In the US, the number of registrations is more compared to other countries, but this rise in the registration of clinical trials has stagnated over the last couple of years.

The majority of the clinical trials are not specific to gender (Table **3**). Trials included both male and female volunteers. However, data reveals that few of the clinical trials are gender-specific, and the trial includes volunteers of just a specific gender. Data were exported separately for "only male" and "only female" and processed for text mining. However, as this number is minimal, they can be studied individually. Of India's 127 clinical trials, none showed any gender-specific study. It may be because gender is not specified in India's clinical trials, or there is an issue at the ICTRP level in data retrieval. The possibility of the latter is high.

Analysis of the availability of results as "yes" or "no" in the data revealed the shocking fact of clinical trials on tuberculosis (Fig. **7**). Only 87 of the registered clinical trials are available with their results, out of 1635 registered clinical trials. It may also conclude that only 5.32 percent of registered clinical trials are completed. Even if we disregard the newly registered clinical trials of the last five years (2015 to 2019), only 73 (8.1 percent) of the 901 registrations by 2014 have been completed, and their results are available at IRCTP. A news article [27] from the American Association for the Advancement of Sciences (AAAS) posted by ScienceMag ® also criticizes similar findings. The unavailability of clinical trials' results was also questioned at different platforms [28, 29]. This conclusion, however, is based solely on data exported from IRCTP. At the ICTRP level, there could be a significant chance of error in the data. We found a few ChiCTR clinical trials, the results of which are available on their portal but are not reflected or updated as "yes" in ICTRP. Such an error needs to be addressed and resolved imperatively. Otherwise, the ICTRP's crux motive will eventually be compromised. Even if such an error may exist at the end of ICTRP, it is still true that the percentage of completed clinical trials is substantially low compared to total registered clinical trials. In our independent search at clinicaltrials.gov (US National Library of Medicine), we found that by the end of 2019, only 98 trials had been tagged as completed out of 1055 registered clinical trials.

In clinical trials, the majority of types of studies are either interventional or observational. However, the types of studies are not limited to just these two. Chinese clinical trials represent a gamut of study types other than these two. These include diagnostic testing, epidemiological research, research into relative factors, basic science, research on health services, the study of treatment, screening, research on prognosis, prevention, and causes. To understand the exact meaning of these types of studies, one must explore the Chinese Clinical Study Registry website. In each country, the number of interventional studies is much more than the number of observational or other studies, as shown in Fig. (**8**).

Entries in the column labeled as "phase" were refined manually using Microsoft Excel®. This manual refinement was required as multiple aliases were utilized for the same phase of the clinical trial. For instance, "Phase-4"; "Phase4"; "Phase IV"; "IV" and simply "4" were utilized to represent phase - 4. Many other terms, like basic science, other, phase 0, pilot study, and post-market, are also found

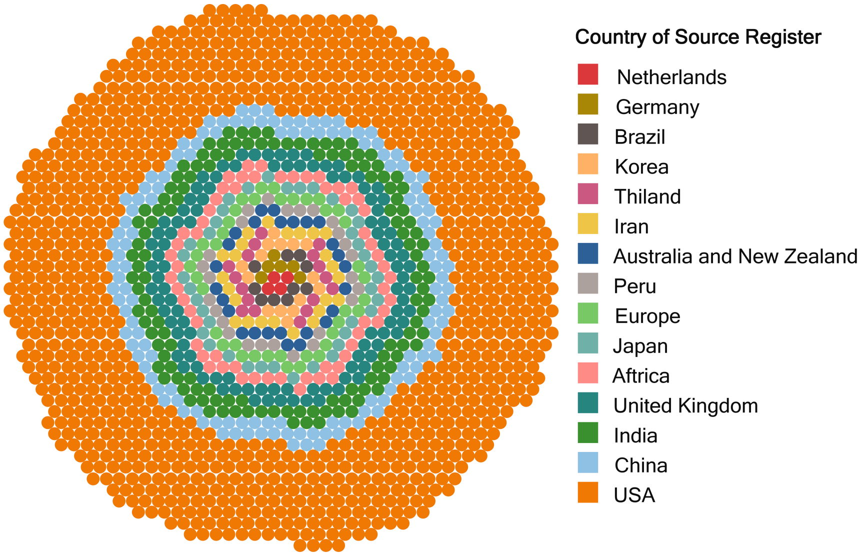


Fig. (5). Country (source register) wise contribution to tuberculosis clinical trials. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

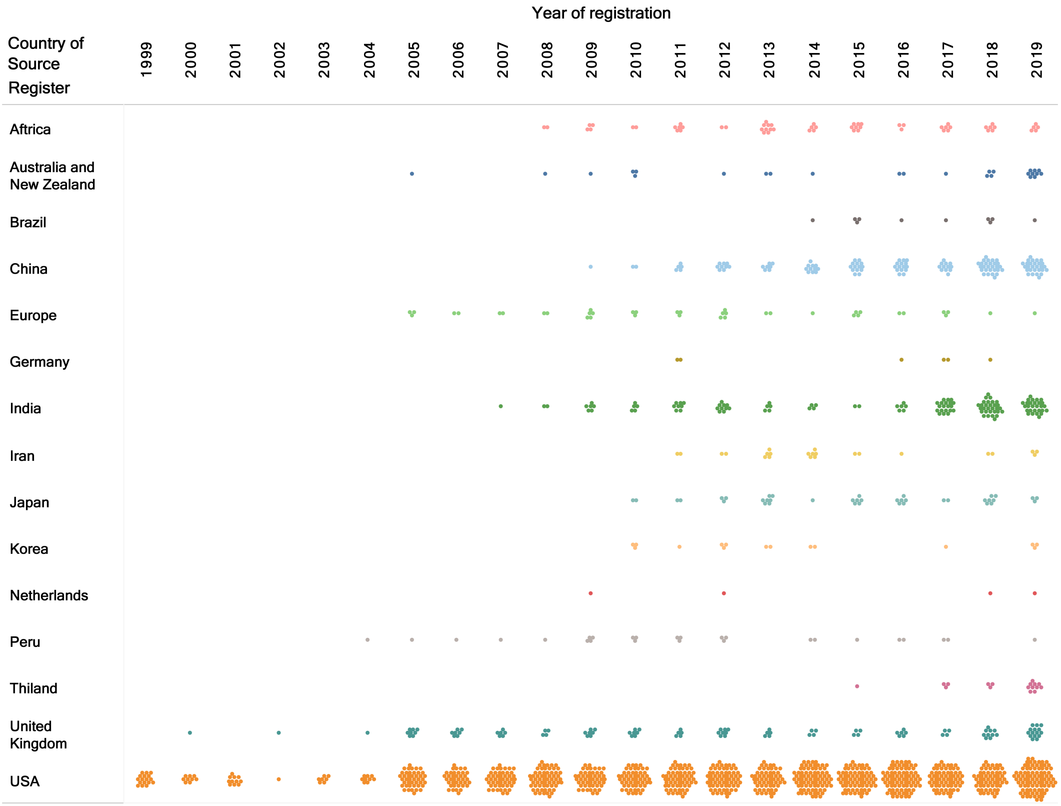


Fig. (6). Year-wise contribution of each country to tuberculosis clinical trials. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 3. Distribution of inclusion gender of the volunteers in clinical trials of tuberculosis.

Source Register	Number of Registrations n (% of Total)	Inclusion Gender			
		Only Male	Only Female	Both	Not Specified
ANZCTR	26 (1.59)	1	1	24	-
ChiCTR	132 (8.07)	6	1	122	3
NCT	1008 (61.65)	28	30	950	-
CRIS	15 (0.92)	-	-	15	-
CTRI	127 (7.77)	-	-	-	127
EUCTR	39 (2.39)	-	-	39	-
DRKS	6 (0.37)	-	-	6	-
IRCT	24 (1.47)	1	-	23	-
ISRCTN	103 (6.03)	-	2	97	4
JPRN	39 (2.39)	-	-	39	-
NTR	4 (0.24)	-	-	-	4
PACTR	59 (3.61)	2	1	56	-
REBEC	10 (0.61)	1	-	-	9
REPEC	26 (1.59)	-	-	15	11
TCTR	17 (1.04)	-	-	17	-

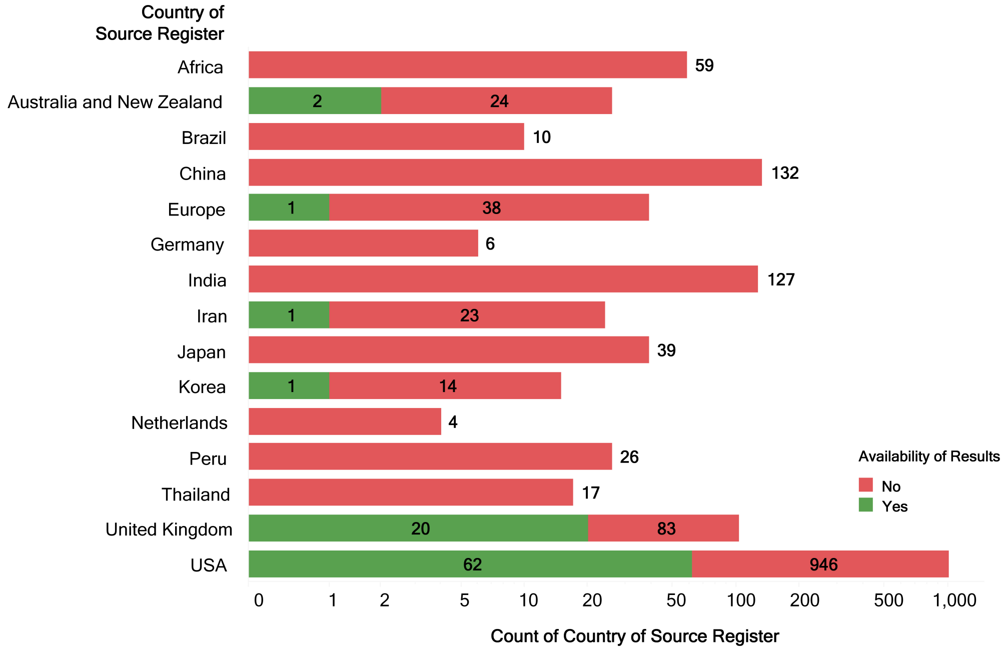


Fig. (7). Country-wise availability of results for registered clinical trials on tuberculosis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

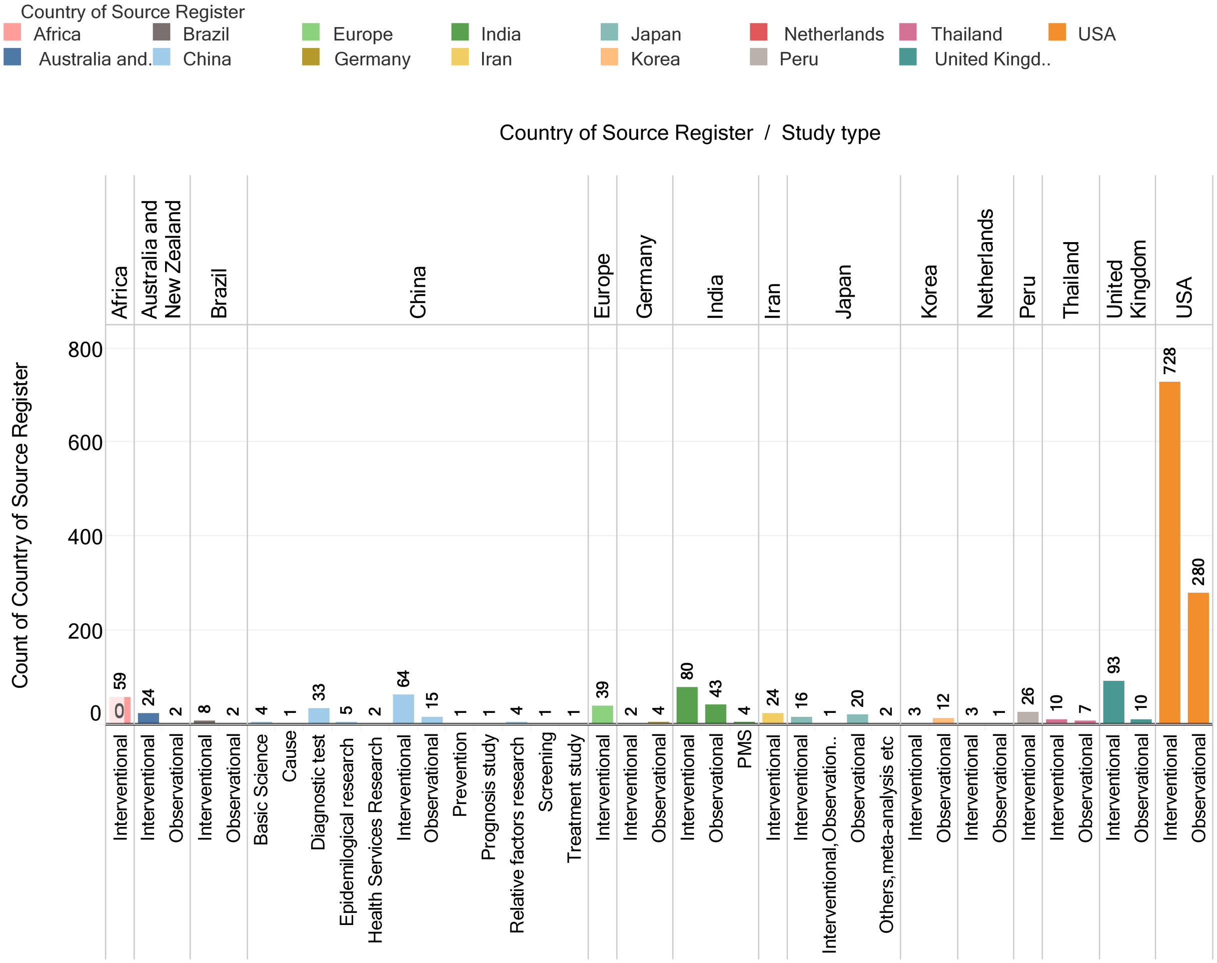


Fig. (8). Country-wise study of tuberculosis clinical trials.

Table 4. Country-wise status of phases of tuberculosis clinical trials.

Country of Source Register	% Phase of total clinical trial (% Phase of the total clinical trial of the individual country)				
	Phase-4	Phase-3	Phase-2	Phase-1	Other
Africa	0.06 (1.69)	0.12 (3.38)	0.36 (10.1)	0.06 (1.69)	2.99 (83.0)
Australia and New Zealand	0.18 (11.5)	0.18 (11.5)	0.06 (3.84)	0.00 (0.00)	1.16 (73.0)
Brazil	0.12 (20.0)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.48 (80.0)
China	0.48 (6.06)	0.12 (1.51)	0.06 (0.75)	0.55 (6.81)	6.85 (84.8)
Germany	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.06 (16.6)	0.30 (83.3)
Europe	0.00 (0.00)	0.30 (13.5)	0.48 (21.6)	0.00 (0.00)	1.46 (64.8)
India	0.48 (6.20)	1.10 (13.9)	1.03 (13.1)	0.42 (5.42)	4.83 (61.2)
Iran	0.06 (4.16)	0.30 (20.8)	0.00 (0.00)	0.00 (0.00)	1.10 (75.0)
Japan	0.12 (5.12)	0.06 (2.56)	0.06 (2.56)	0.06 (2.56)	2.07 (87.1)
Korea	0.06 (6.66)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.85 (93.3)
Netherland	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.24 (100)
Peru	0.30 (19.2)	0.67 (42.3)	0.61 (38.4)	0.00 (0.00)	0.00 (0.00)
Thailand	0.12 (11.7)	0.30 (29.4)	0.12 (11.7)	0.00 (0.00)	0.48 (47.0)
United Kingdom	0.18 (2.91)	0.42 (6.79)	0.06 (0.97)	0.06 (0.97)	5.56 (88.3)
USA	5.25 (8.53)	6.72 (10.9)	12.1 (19.7)	11.7 (19.0)	25.7 (41.7)
Total % of Phase	7.46	10.3	15.0	12.9	54.1

in this column, commonly regarded as “Other” in Table **4**. This analysis reveals that only 7.46 percent of total registered clinical trials are phase-4 trials. Particularly for India, the percentage of phase-4 trials is higher than in other phases. It seems optimistic and hopeful for a meaningful outcome. However, none of these eight clinical trials has reported any results yet. The Trial IDs of them are: (1) CTRI/2009/091/000476; (2) CTRI/2009/091/000511; (3) CTRI/2012/06/002742; (4) CTRI/2012/11/003088; (5) CTRI/2012/11/003155; (6) CTRI/2013/07/003830; (7) CTRI/2017/04/008329; (8) CTRI/2017/09/009693.

3.2. Text Mining

As shown in Fig. (**9**), a huge pool of 17,825 words with 31,920 tokens from the corpus of clinical trials for tuberculosis were generated after preprocessing of text. In this pool, the word "HIV" (n=519) has the highest count, followed by the words "pulmonary" and "phase" (n=510 and 484), respectively. Similarly, it was found that a total of 173 drugs are listed in clinical trials after appropriate preprocessing for the drugs involved in the clinical trials (Fig. **10**). The most common name for the drug is "isoniazid," followed by "rifampicin" and "rifapentine."

3.2.1. Hierarchical Cluster Analysis

As shown in Fig. (**11**), a total of 41 clusters were identified and selected for further analysis *via* the hierarchical clustering technique.

The supplementary table (Table **1**) in the appendix represents the research interest of clinical trials of every cluster in a comprehensive manner. Out of 41 clusters, only seven clusters need sub-clustering to understand the research interest of their clinical trials. Thirty-three (33) clusters, for which successful mapping of the research area was performed, covering 1015 (Supplementary Table **2**) clinical trials out of a total of 1635. The remaining 620 clinical trials, consisting of C27, C29, C32, C34, C35, C37, and C40, may be mapped by sub-clustering for their research interest. This sub-clustering and analysis are not shown here since it can extend the usual publication limit.

In the supplementary table (Table **1**), the research interests or areas mapped for 1015 clinical trials are summarized and shown in Table **5**. As per this summary, the highest number of TB clinical trials are focused on HIV infection. In addition to common research trends on HIV, vaccine, BCG, MDR, *etc*., other interesting research trends including vitamins, active case findings in the community, diabetes, pleural effusion, fixed-dose combinations, meningitis, *etc*. are also mapped.

Cluster 35 contains 384 clinical trials for which the mapping of research interest is not possible without sub-clustering. Sub-clustering of C35 (similar to hierarchical clustering) and the selection of 80% of the total height of the dendrogram have grouped these 384 clinical trials in 14 different Sub-clusters. As shown in Fig. (**12**), these 14 subclusters have a positive silhouette score. It means the mapping of research areas for these clusters is possible with excellent resolution. The research area of 8 clusters out of these 14 was identified and listed in Table **6**. Rest can be easily mapped through re-reclustering (not shown here).

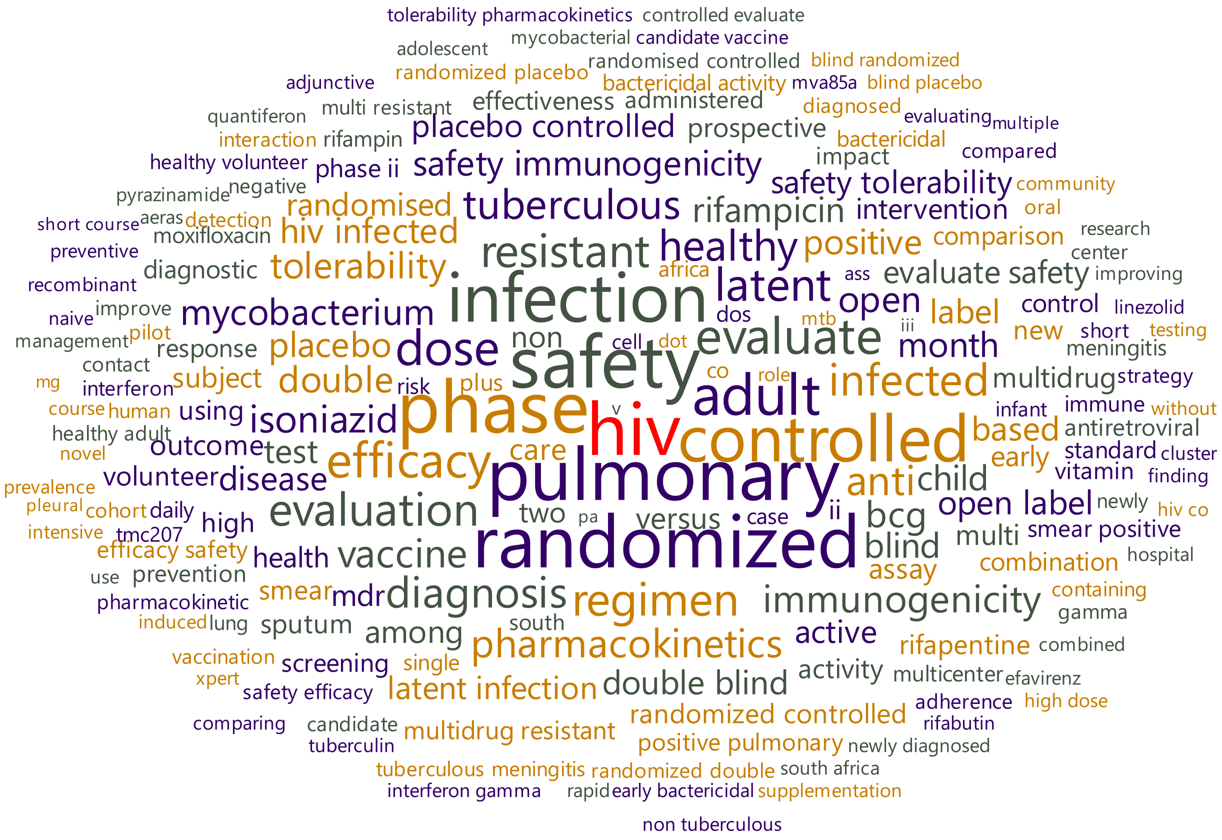


Fig. (9). Word cloud of text from tuberculosis clinical trials. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

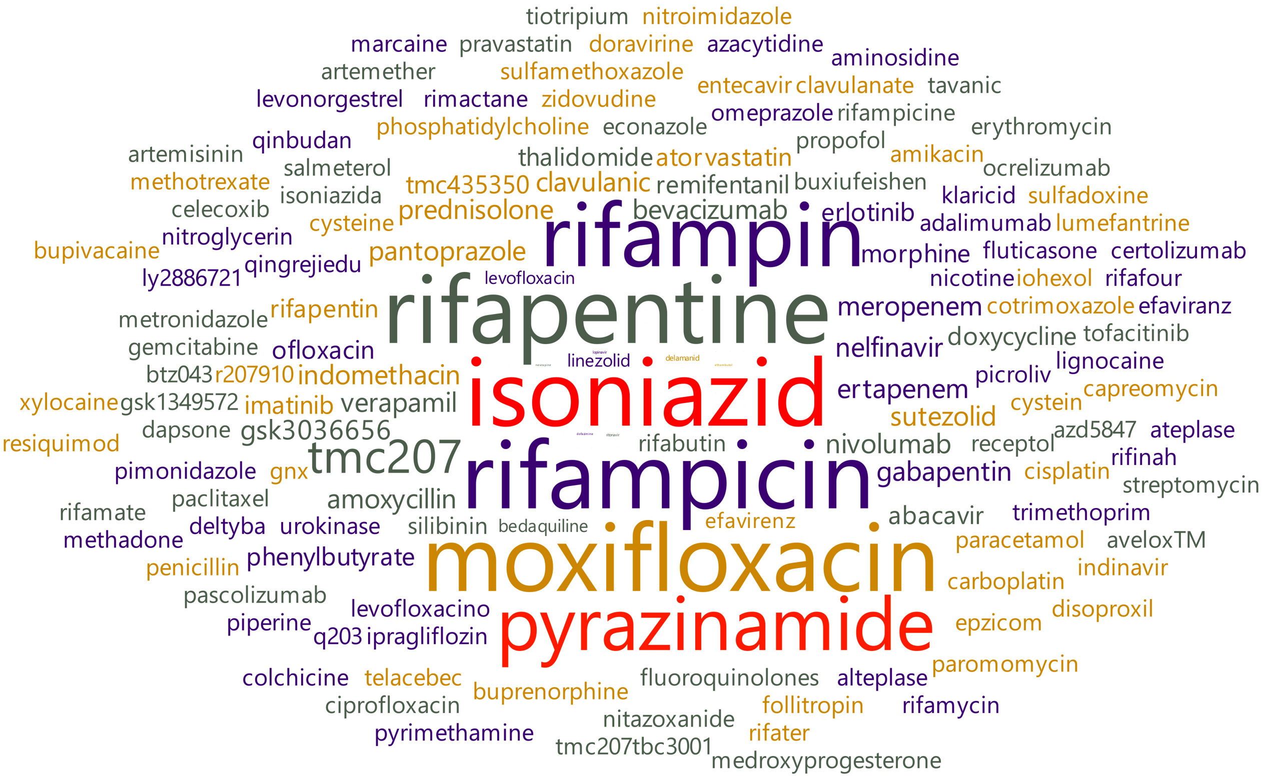


Fig. (10). Word cloud of drugs mentioned in tuberculosis clinical trials. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

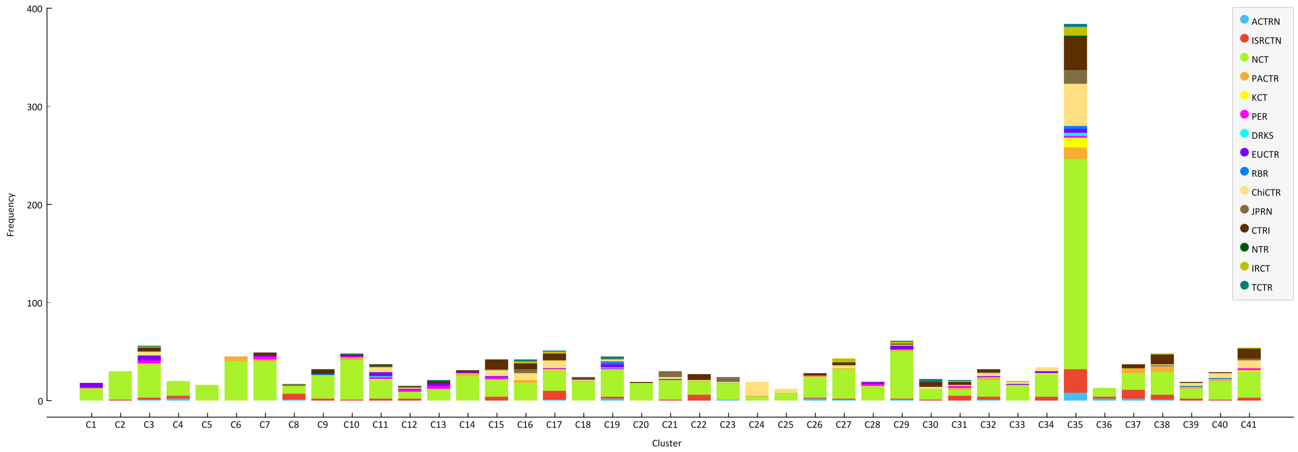


Fig. (11). Hierarchical cluster distribution. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 5. Summary of research interests derived from the hierarchical cluster analysis.

Sr. No	Common Research-Interest / Trend / Area, Which Represents the Entire Cluster	Number of Clinical Trials*
1.	Vaccine and Immunological Studies	234
2.	Placebo related studies	56
3.	BCG related studies	20
4.	HIV and other co-infection related studies	292
5.	MDR related studies	104
6.	Bacteriocidal activities of compound	31
7.	Regimen related studies	42
8.	Pulmonary tuberculosis related studies	42
9.	Diabetes and tuberculosis related studies	12
10.	Diagnostic related studies	86
11.	Latent tuberculosis related studies	45
12.	Meningitis related studies	27
13.	Non-tuberculosis Mycobacteria related studies	24
14.	Plural effusion related studies	19
15.	Recombinant products related studies	12
16.	Isoniazid related studies only	28
17.	Rifapentine, Moxifloxacin, and Rifabutin related studies	20
18.	Pharmacokinetic and toxicity of various anti-TB agents	104
19.	Directly Observed Therapy (DOT) related studies	22
20.	Fixed-Dose Combination related studies	21
21.	Role of Vitamins related studies	20
22.	Studies related to Active Case Finding in various communities	13
23.	Quality of Health and Life-related studies	48
24.	Xpert MTB-RIF assay related studies	19
25.	lipoarabinomannan (LAM) assay related studies	06

(* numbers of clinical trials in a particular cluster).

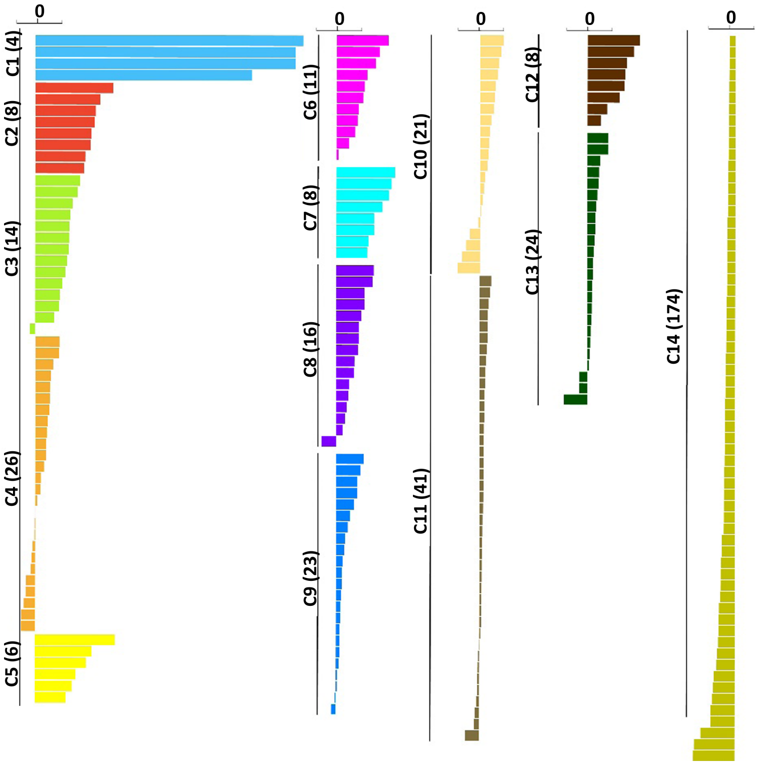


Fig. (12). Silhouette plot of subclusters of C35. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 6. Research area mapped to C35 *via* sub-clustering.

Sr. No	Common Research-Interest / Trend / Area, Which Represents the Entire Cluster	Number of Clinical Trials*
1.	Early mortality related studies	4
2.	Low birth weight / weight (in TB) related studies	8
3.	Diagnostics related studies	14
4.	Screening and tracing related studies	26
5.	Smoking-related studies	6
6.	South-africa specific studies	11
7.	Cohort Studies	8
8.	Surgeries and Tuberculosis related studies	8

CONCLUSION

Data Mining

Overall, data mining suggests that clinical trials for tuberculosis should be focused more on the new drug, new regimen, and more specifically on MDR-TB to be prepared for the possibly upcoming disaster with TB. It is also crucial to publish the results of every registered clinical trial as soon as possible to boost knowledge about tuberculosis in the research community. A provision should be explored regarding the current status of the registered clinical trial and the probable date of its completion. Countries other than the US must considerably increase their contribution to tuberculosis research and clinical trials.

Text Mining

Comprehension of the research pattern manually from a large number of clinical trials is a complicated job. Text mining is indeed a convenient approach for understanding any disease from registered clinical trials. For the research fraternity with nonprogramming background, the use of GUI-based open-source software for text mining and clinical trial analysis is quite simple. The research-interest mapping method explained here can be easily reproduced for any clinical trial dataset exported from ICTRP and other registries. This mapping technique can enable researchers to understand the overall areas of research where clinical trials are initiated. In this work, we have mapped 23 different research areas/topics in which tuberculosis clinical trials are registered worldwide. The conventional method of manually reviewing pieces of literature cannot be employed when the number is large. It is even tedious and intricate to review literature like clinical trials if their numbers are exceedingly more than a hundred. This article reviews over 1600 pieces of literature in order to obtain an overview. In essence, text-mining is the best approach to perform a literature review. The GUI-based open-source tool can be easily used by researchers with a non-programming background.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

APPENDIX

VBA CODE FOR EXPORT OF EACH ROW IN .TXT FILE FORMAT

```
Sub SaveRowsAsTXT()
Dim wb As Excel.Workbook, wbNew As Excel.Workbook
Dim wsSource As Excel.Worksheet, wsTemp As Excel.Worksheet
Dim r As Long, c As Long
Dim filePath As String
Dim fileName As String
Dim rowRange As Range
Dim cell As Range
filePath = "C:\Tuberculosis\"
For Each cell In Range("B1", Range("B10").End(xlUp))
Set rowRange = Range(cell.Address, Range(cell.Address).End(xlToRight))
Set wsSource = ThisWorkbook.Worksheets("Sheet1")
Application.DisplayAlerts = False 'will overwrite existing files without asking
r = 1
Do Until Len(Trim(wsSource.Cells(r, 1).Value)) = 0
ThisWorkbook.Worksheets.Add ThisWorkbook.Worksheets(1)
Set wsTemp = ThisWorkbook.Worksheets(1)
For c = 2 To 25
wsTemp.Cells((c - 1) * 2 - 1, 1).Value = wsSource.Cells(r, c).Value
Next c
fileName = filePath & wsSource.Cells(r, 1).Value
wsTemp.Move
Set wbNew = ActiveWorkbook
Set wsTemp = wbNew.Worksheets(1)
wbNew.SaveAs fileName & ".txt", xlTextWindows 'save as .txt
wbNew.Close
ThisWorkbook.Activate
r = r + 1
Loop
Application.DisplayAlerts = True
Next
End Sub
```

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