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Interpretable Clinical Trial Search using Pubmed Citation Network

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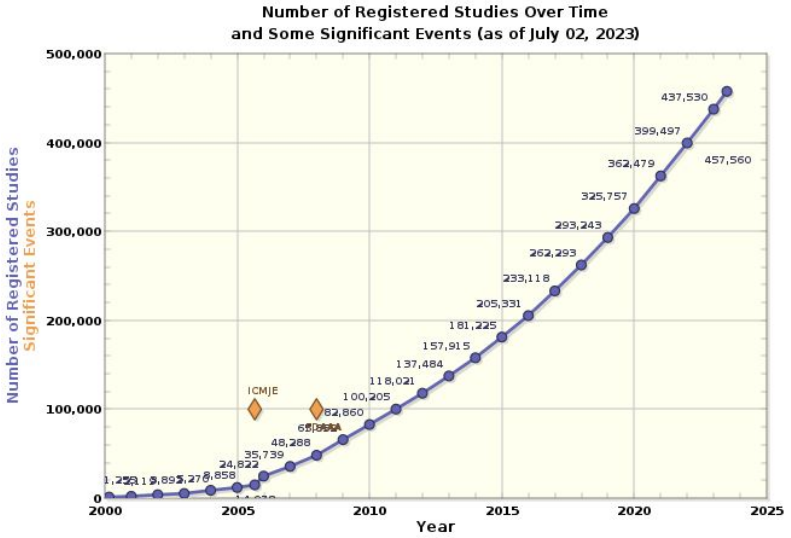
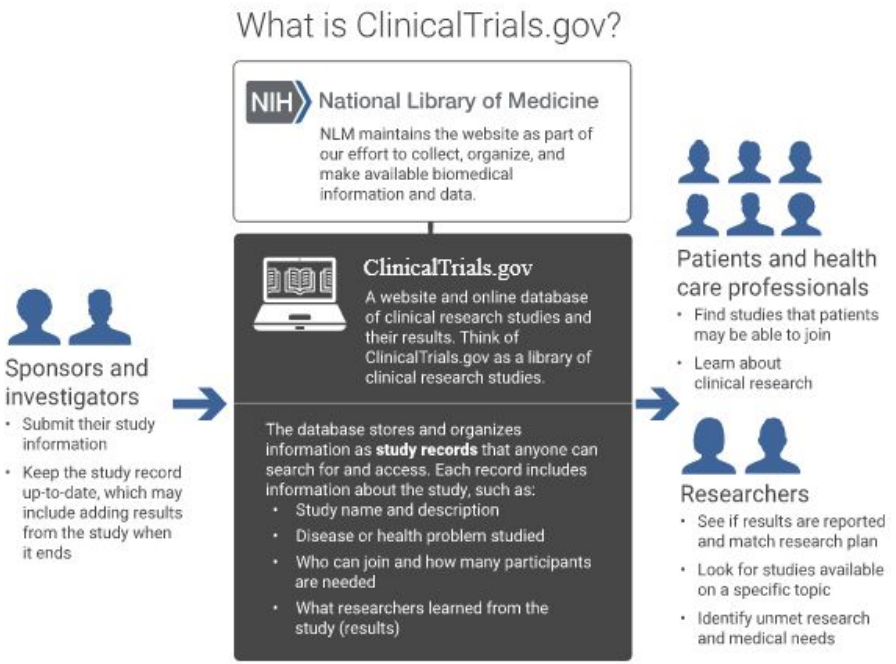
Why are clinical trials important ?

- Clinical trials provide the earliest source of information about new drugs and treatments
- Clinical trial search systems help meet the information need, given the rising volume of clinical trials and related publications



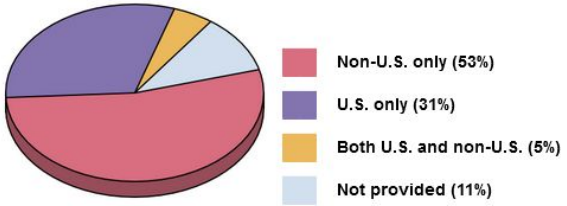
Source: https://ClinicalTrials.gov

Clinical Trial Search - Document Collection



Percentage of Registered Studies by Location (as of July 02, 2023)

Total of 457,560 studies

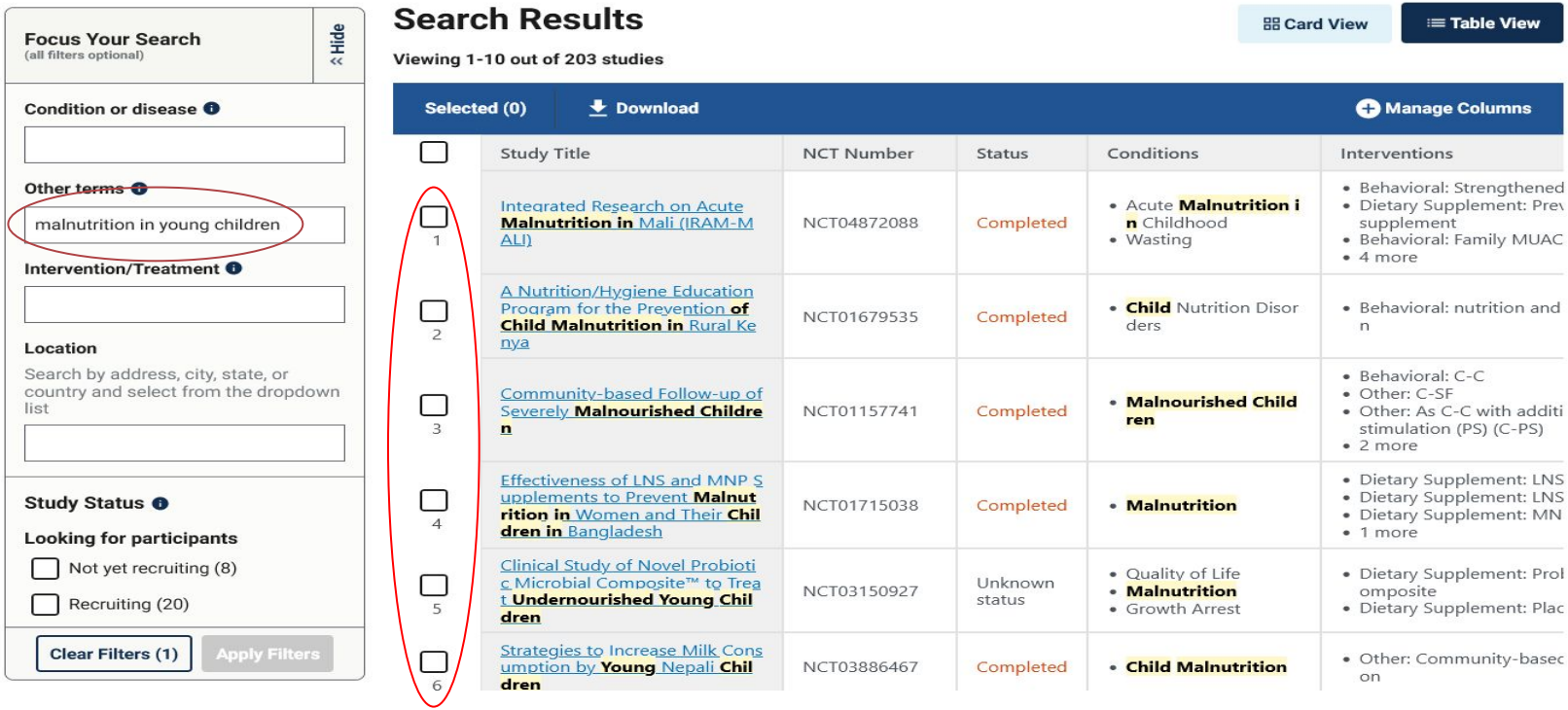


Location	Number of Registered Studies and Percentage of Total (as of July 02, 2023)
Non-U.S. only	244,005 (53%)
U.S. only	141,320 (31%)
Both U.S. and non-U.S.	22,390 (5%)
Not provided	49,845 (11%)
Total	457,560 (100%)

Source: https://clinicaltrials.gov/about-site/about-ctg

https://classic.clinicaltrials.gov/ct2/resources/trends

Clinical Trial Search - Query and Ranking



Focus Your Search
(all filters optional)

Hide

Condition or disease

Other terms

malnutrition in young children

Intervention/Treatment

Location

Search by address, city, state, or country and select from the dropdown list

Study Status

Looking for participants

- Not yet recruiting (8)
- Recruiting (20)

Clear Filters (1) | Apply Filters

Search Results

Viewing 1-10 out of 203 studies

Card View | Table View

Selected (0) | Download | Manage Columns

	Study Title	NCT Number	Status	Conditions	Interventions
1	Integrated Research on Acute **Malnutrition in** Mali (IRAM-MALI)	NCT04872088	Completed	• Acute **Malnutrition i n** Childhood • Wasting	• Behavioral: Strengthened • Dietary Supplement: Prev supplement • Behavioral: Family MUAC • 4 more
2	A Nutrition/Hygiene Education Program for the Prevention **of Child Malnutrition in** Rural Kenya	NCT01679535	Completed	• **Child** Nutrition Disorders	• Behavioral: nutrition and n
3	Community-based Follow-up of Severely **Malnourished Children**	NCT01157741	Completed	• **Malnourished Child ren**	• Behavioral: C-C • Other: C-SF • Other: As C-C with additi stimulation (PS) (C-PS) • 2 more
4	Effectiveness of LNS and MNP Supplements to Prevent **Malnutrition in** Women and Their **Children in** Bangladesh	NCT01715038	Completed	• **Malnutrition**	• Dietary Supplement: LNS • Dietary Supplement: LNS • Dietary Supplement: MN • 1 more
5	Clinical Study of Novel Probiotic Microbial Composite™ to Treat **Undernourished Young Children**	NCT03150927	Unknown status	• Quality of Life • **Malnutrition** • Growth Arrest	• Dietary Supplement: Prol omposite • Dietary Supplement: Plac
6	Strategies to Increase Milk Consumption by **Young** Nepali **Children**	NCT03886467	Completed	• **Child Malnutrition**	• Other: Community-basec on

Source: https://clinicaltrials.gov/search?term=malnutrition%20in%20young%20children&viewType=Table (as of July 4, 2023)

Key Takeaways

- MPSS can be used to perform clinical trial search across all disease classes
    - TREC Precision Medicine Track (2017 to 2020) focused only on cancer-related trials

Key Takeaways

- Contribute an evaluation dataset of 25 queries with trials marked as relevant or non-relevant to the given query
  - Around 95 trials per query are annotated
  - Queries range over five-most frequent MeSH disease classes in document collection:
    - Pathological Conditions, Signs & Symptoms; Cardiovascular Diseases; Nervous System Diseases; Nutritional and Metabolic Diseases; Immune System Diseases

Key Takeaways

- MPSS focus on ordinary users (patients or consumers) and thus the nature of our queries are free-form text
  - TREC PM track had a fixed schema, with fields like gene and mutation information, which is very specific to cancer-related trials

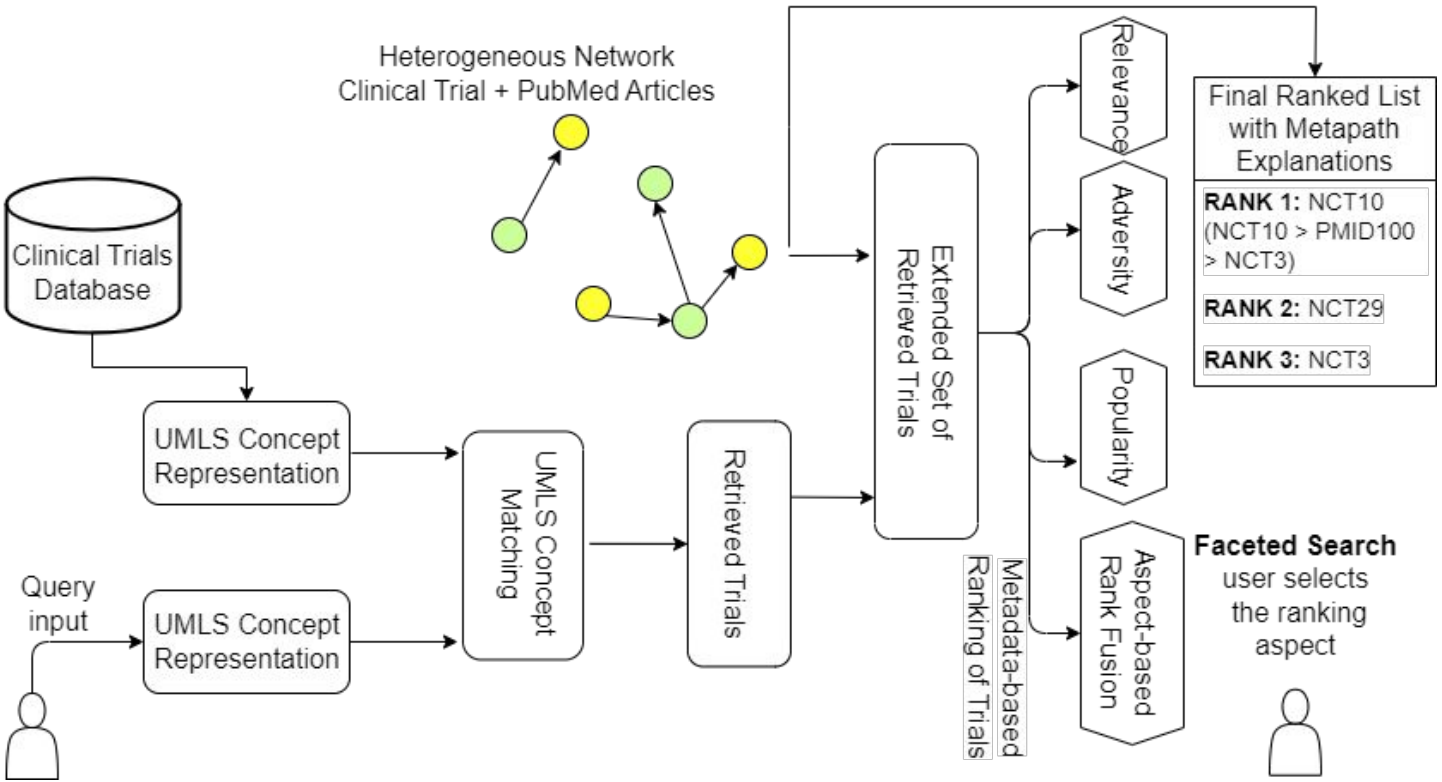
```
<topics task="2018 TREC Precision Medicine">
 <topic number="1">
  <disease>Acute lymphoblastic leukemia</disease>
  <gene>ABL1, PTPN11</gene>
  <demographic>12-year-old male</demographic>
 </topic>
 ...
</topics>
```

Source: http://trec-cds.org/2018.html

Key Takeaways

- We construct a novel heterogeneous information network of both clinical trials and linked Pubmed articles to alleviate sparsity issue
    - Difficult to find direct links between two clinical trials
- Explore a path-based retrieval approach that becomes explainable to the end users
- Provide a combined ranking scheme based on relevance, adversity and popularity
- Develop strategy to adapt MPSS to the TREC PM task that deals with only cancer trials

Detailed methodology of MPSS



AACT-DB: Clinical Trials Corpus

- Consists of 331,713 clinical trials (May 2020 snapshot)
  - Made available through Clinical Trials Transformation Initiative, https://aact.ctti-clinicaltrials.org/
- Select trials with at least one linked Pubmed article
- Select trials from top five most frequent disease classes

Trial ID	NCT00000106	
Brief Title	Whole Body Hyperthermia for the Treatment of Rheumatoid Disease	
MeSH Term	Rheumatoid Diseases	Hyperthermia
MeSH Tree	C05.799	C23.888.119.455
Disease class	Musculoskeletal Diseases	Pathological Conditions, Signs and Symptoms

Creation of Query-Relevant Trial Set

- 25 queries with 95 trials per query with relevance annotation
- Query Preparation: Five from each disease class
    - **Representative of real-life queries:** Templates from Patel et al. (2010) who observed it from user logs from TrialX search engine:

(2010). What do patients search for when seeking clinical trial information online?. In AMIA Annual Symposium Proceedings (Vol. 2010, p. 597). American Medical Informatics Association.

Creation of Query-Relevant Trial Set

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- Query Preparation: Five from each disease class
  - **Representative of real-life queries:** Templates from Patel et al. (2010) who observed it from user logs from TrialX search engine:
    - (Disease or syndrome) + (symptom or treatment): *dietary approaches for obesity treatment*
    - Disease + age group: *managing constipation in children*
    - Disease + safety information: *safe treatment for Alzheimer disease*

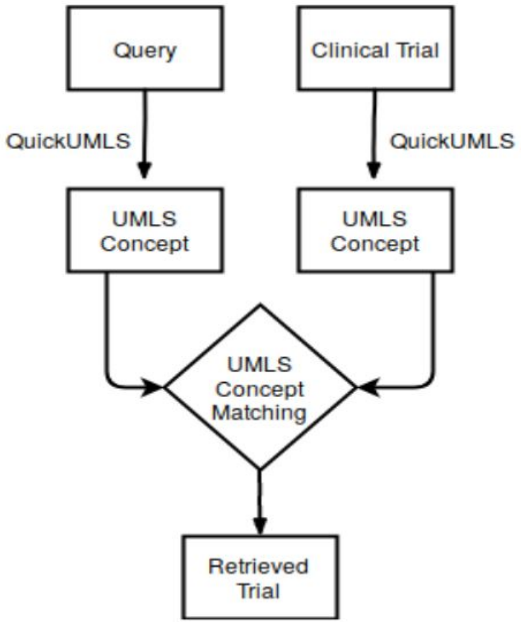
(2010). What do patients search for when seeking clinical trial information online?. In AMIA Annual Symposium Proceedings (Vol. 2010, p. 597). American Medical Informatics Association.

Queries divided based on "safety" aspect

- **Type-1**: when query mention safety requirements, the search system should prioritize trials with no reported adverse events
  - Example: *safe treatments for asthma*
  - Develop manually curated lexicon set containing words like *safe, safety* and use exact matches to maintain high precision
- **Type-2**: all the remaining queries
  - Example: *haemorrhage cure, Early Parkinson disease treatment*

Clinical trial retrieval: Match-based retrieval

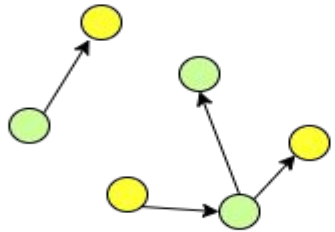
For a query 'q', we retrieve all the trials whose (brief title + official title + brief summary) contain all the UMLS concept ids that are present in 'q'



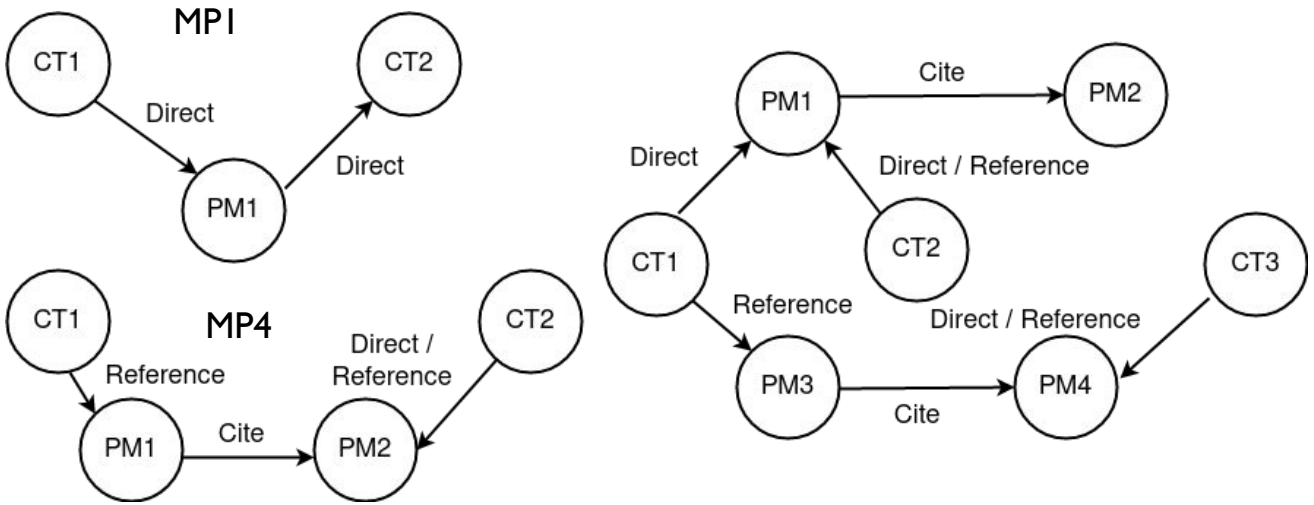
Luca Soldaini and Nazli Goharian. Quickumls: a fast, unsupervised approach for medical concept extraction

Heterogeneous Information Network Construction

- Two node types: Clinical Trial (CT) and Pubmed article (PM)
- Three edge types:
  - **Direct:** Pubmed article published for a CT after its completion
  - **Reference:** PM acts as reference or result references of a CT
  - **Cite:** PM is linked to their citations to other PM's



Heterogeneous Information Network Construction



Subgraph samples. Comprises of 750K nodes and 1.2 million edges. Clinical trial nodes are sparsely connected (8.36% nodes are of clinical trials, rest are Pubmed articles

Proposed Metapath-based Similarity Search

- One-time computation that computes the similarity set SimSet(CT) for each clinical trial in the corpus
- Empirically determine maximum SimSet Size by balancing the coverage (recall) and quality of new retrieved trials (precision)

Restriction Type	MP1	MP2	MP3	MP4	MP5	MP6
Most restricted	✅	✅	✅		✅	
Moderate	✅	✅	✅	✅	✅	
Most Relaxed	✅	✅	✅	✅	✅	✅

Multiple stakeholders = Multiple ranking aspects

- Explore the "faceted search paradigm"
- Individual ranking aspects: **Relevance, Adversity, Popularity**
- Aspect-based rank fusion to obtain a single ranked list (Variations)
  - **MetaRRF**: All ranking aspects are given same weightage
  - **MetaADV**: More weightage to adversity aspect
  - **MetaCOMB** (proposed): Use MetaADV for Type-1 queries and MetaRRF for Type-2 queries

Adaptation to TREC 2018 Precision Medicine Track

Query	Disease: *melanoma*, Gene (Variant): *BRAF (V600E)*, Demographic: *64-year-old male*
Gene Name	BRAF (Entrez Gene Id: 673)
Variant	V600E
Gene Description	B-Raf proto-oncogene, serine / threonine kinase
Gene Synonyms from NCBI Gene	NS7, B-raf, BRAF1, RAFB1, B-RAF1
Interacting Drugs from DGIdb	Pictilisib bismesylate, panobinostat, binimetinib, oxaliplatin, fostamatinib, …

Adapting Relevance Ranking for TREC-PM task

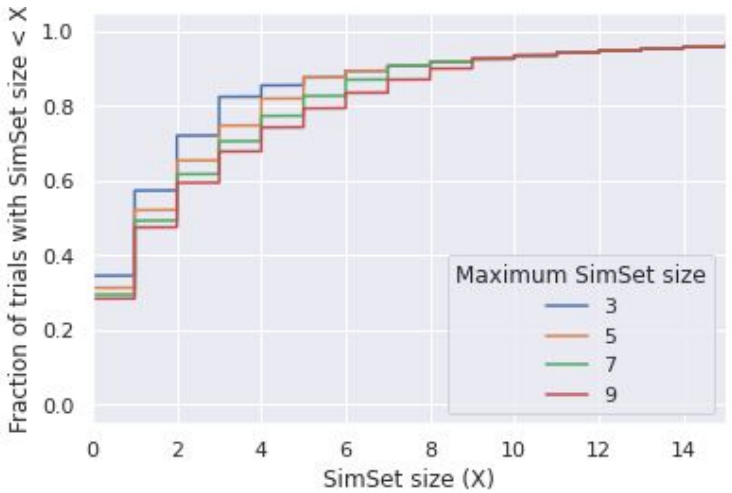
- Sort the trials in non-increasing order of "Gene relevance", and continue with stable sorting in the following order
  - Term frequency of Mutation, Gene, Gene synonyms
  - PageRank score among retrieved set of trials

Evaluation Setup

- Evaluation metric: Precision at ranks 5, 10, 15 and 20
  - Precision and nDCG score
  - Cannot measure recall due to lack of complete retrieved set of clinical trials for each query
- Evaluation datasets - MPSS is trained in unsupervised manner
  - Disease-independent Evaluation Dataset (25 queries)
  - TREC 2018 Precision Medicine Benchmark Dataset (50 queries)

Performance Evaluation of Retrieval Stage

- Higher values of maximum SimSet size (maxSS) proportionately improves recall
- Precision@5 and @10 first increases with increase in maxSS, peaks at maxSS=5, and then drops by 33.4% and 37% respectively at maxSS=7



Query Type	Model	P@5	P@10	P@15	P@20
Type-1	MetaRRF	0.6	0.46	0.48	0.5
	MetaADV	0.96	0.92	0.89	0.77
Type-2	MetaADV	0.43	0.46	0.44	0.44
	MetaRRF	0.52	0.53	0.46	0.47
All	BAS	0.12	0.08	0.08	0.08
	STM	0.56	0.52	0.47	0.46
	MetaSTM	0.59	0.56	0.54	0.52
	MetaRRF	0.54	0.51	0.47	0.48
	MetaADV	0.54	0.55	0.53	0.51
	MetaCOMB	0.62	0.60	0.55	0.54

MetaCOMB outperforms the baselines models in terms of P@5, P@10, P@15 and P@20

Performance Evaluation of Ranking Stage

- Aspect-based rank fusion does not reduce the quality of search
  - MetaCOMB performs comparably with MetaSTM (relevance only)
- Metapath-based similarity search helps improve clinical trial search performance
  - MetaSTM outperforms STM (its non-metapath version) at all ranks; the performance increases as we move from rank 5 to rank 20
- Query representation by UMLS concepts is more flexible than lexical matches and accommodates query variations

Performance Evaluation of Ranking Stage

- Giving equal weightage to all ranking aspects irrespective of the type of queries fails
- MetaADV (more weightage to adversity aspect) achieves very high precision@10 ~ 0.9 for **Type-1 queries,** outperforming MetaRRF
- MetaRRF performs better than MetaADV for Type-2 queries

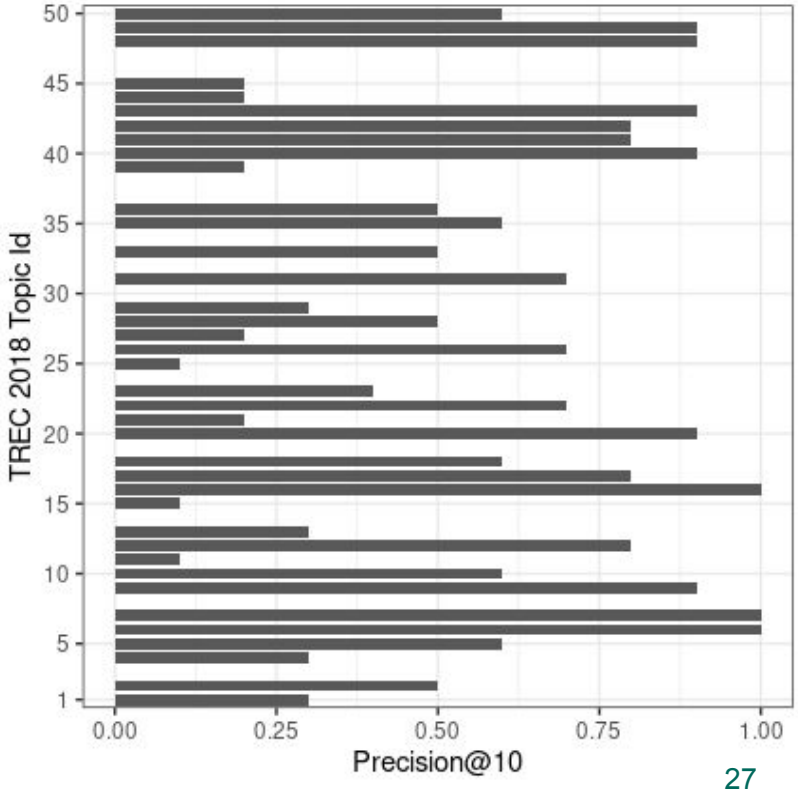
TREC 2018 Adaptation Results

- MPSS achieves precision at ranks one, two and five of 0.5, 0.42, and 0.46 respectively
- MPSS is purely unsupervised and do not use 2017 TREC-PM training data
- MPSS does not utilize do not utilize disease-specific knowledge bases like COSMIC

Model	P@10	R-Prec	infNDCG
Cat_Garfield	**0.626**	**0.429**	**0.550**
ims_unipd	0.566	0.413	0.540
UTDHLTRI	0.538	0.368	0.479
MPSS	0.432	0.303	0.281

TREC 2018 Adaptation Ablation Results

- Addition of drug interactions and gene-drug linked publications data improves Precision@10 by 9.75%
- Addition of adapted gene relevance further improved Precision@10 by 9.64%, thus achieving 0.432



Conclusion

- Develop a metapath-based similarity search approach, MPSS, for clinical trial search across multiple disease classes
- Construct a heterogeneous information network of both clinical trials and linked Pubmed articles to alleviate the sparsity issue
- Explore the path-based retrieval approach that becomes explainable to the end users

Conclusion

- Provide a combined ranked list based on relevance, adversity, and popularity
- Contribute an annotated (query-relevant trial) retrieval set for 25 queries (95 trials are annotated per trial on average) across five disease classes
- Evaluate MPSS in a zero-shot setting (without any task-specific training) on TREC 2018 Precision Medicine Track

Code and Data Availability

- We make all the codes and data publicly available at https://github.com/roysoumya/MPSS-clinical-trial-search
- Specifically, we contribute a disease-independent evaluation dataset for clinical trial search systems that may encourage more research in this critical domain.

Acknowledgements

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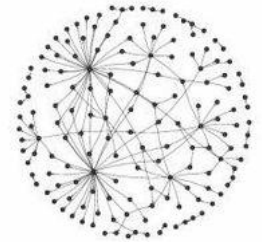
- Complex Networks Research Group, Department of Computer Science and Engineering, IIT Kharagpur (https://cnerg-iitkgp.github.io/)



Acknowledgements

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Thanks for listening

Any Questions?

Please feel free to reach me at: soumyadeep.roy9@iitkgp.ac.in

To know about my current and past projects, please visit datanalytics101.com/

What is a clinical trial ?

NIH defines a clinical trial as:

"*A research study in which one or more* ***human subjects*** *are prospectively assigned to* ***one or more interventions*** *(which may include placebo or other control) to* ***evaluate the effects*** *of those interventions on* ***health-related biomedical or behavioral outcomes***."

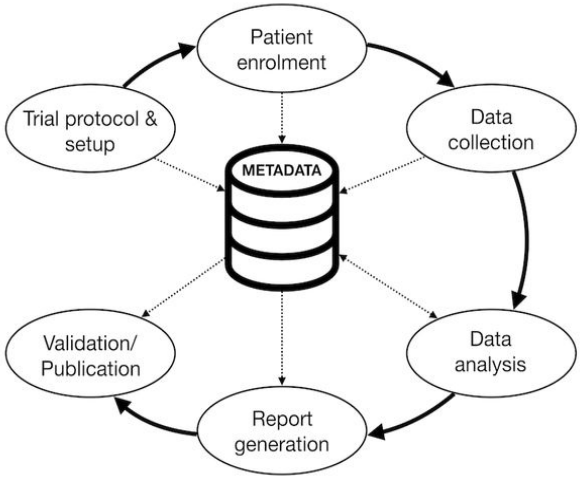
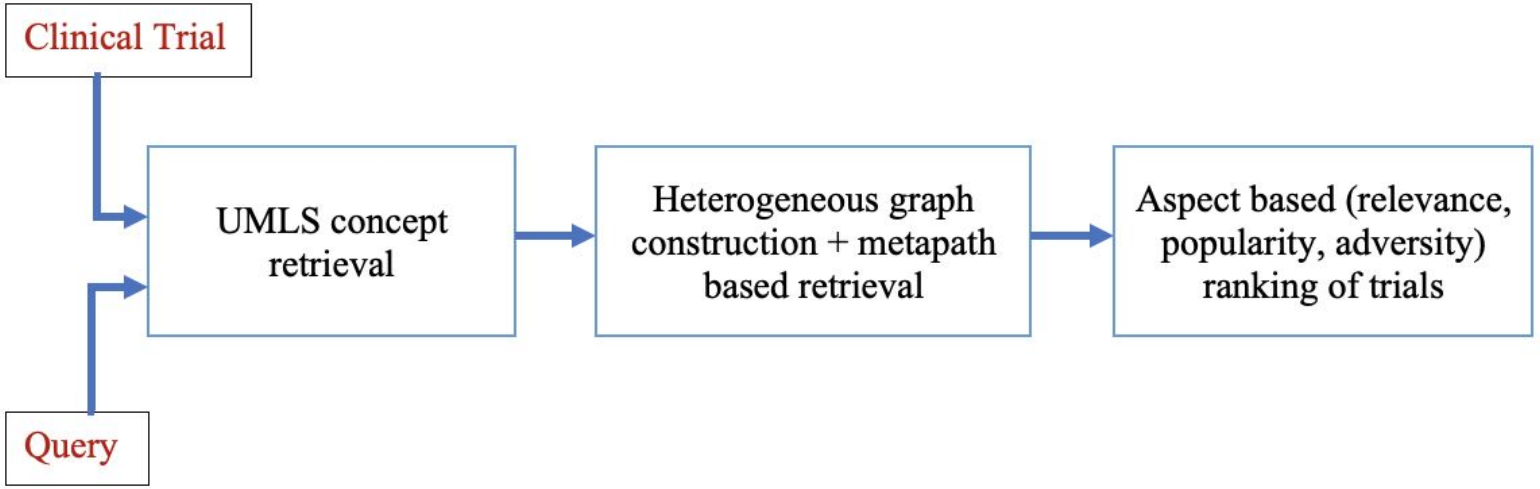


Image source: (2018). Using Blockchain Technology to Manage Clinical Trials Data: A Proof-of-Concept Study. JMIR Medical Informatics. 6. e11949. 10.2196/11949.

MPSS: Interpretable Clinical Trial Search using Pubmed Citation Network



Methodological overview of **M**eta**P**ath-based **S**imilarity **S**earch

Metapath strength - high to low

- Degree of strength between source and target CT node
- MP1 is strongest and MP6 is weakest

Metapath Type	Condition
MP1	$CT \xrightarrow{direct} PM \xrightarrow{direct} CT$
MP2	$CT \xrightarrow{direct} PM \xleftarrow{reference} CT$
MP3	$CT \xrightarrow{reference} PM \xrightarrow{direct} CT$
MP4	$CT \xrightarrow{direct} PM \xrightarrow{cite} PM \xleftarrow{direct/reference} CT$
MP5	$CT \xrightarrow{reference} PM \xleftarrow{reference} CT$
MP6	$CT \xrightarrow{reference} PM \xrightarrow{cite} PM \xleftarrow{direct/reference} CT$

Aspect-based ranking - Adversity

- First ranked in non-decreasing order in terms of number of subjects affected (using the Subjects Affected field)
    - Trials with no reported adverse events are placed at the bottom of the list

Adaptation to TREC 2018 Precision Medicine Track

TREC-PM track contains only cancer trials and their query has a fixed schema containing disease, gene, variant and demographic information

Query	Disease: *melanoma*, Gene (Variant): *BRAF (V600E)*, Demographic: *64-year-old male*

Pubmed-enhanced Retrieval

- Filter the trials based on age and gender field
- Perform concept-based matching (in terms of overlap of UMLS concepts extracted using QuickUMLS tool) between: "disease" field of query and "conditions" field of a clinical trial
- Use regular expression matching to separate "gene" and "mutation" information from the "Variant" field of the query

Pubmed-enhanced Retrieval

- Utilize the Drug-Gene Interaction Database (DGIdb) for identifying Pubmed articles that report drug interactions with a specific gene (identifier: Entrez Gene ID)
- Use our constructed heterogeneous information network to extract clinical trials that have a “Direct” type link with such Pubmed articles

Pubmed-enhanced Retrieval

- As document collection, we only consider trials that are mapped to the "Neoplasms" disease class
- Focusing on only one disease class, enhances the sparsity issue.
- We address it by introducing a new metapath type where we connect two clinical trials that share a common Pubmed article as reference or results reference

Computing Gene Relevance

- Value is 2: when both gene and variant information match
- Value is 1: when only gene matches without the variant information

How to conduct a gene match?

- Step 1: Perform UMLS concept overlap between "Gene" field and clinical trial metadata (brief summary, detailed description, and eligibility criteria). Positive if at least one match is found
- Step 2: If gene match is negative in Step 1, obtain gene synonyms using NCBI gene API
- Step 3: if there is a positive gene match, we then perform an exact match with the "variant" sub-field