Challenges of Clinical Trial Patient Recruitment

$900,000

on average spent on patient recruitment and retention [2]

up to **$8 million/day**

in lost sales due to delays in patient recruitment [4]

50%

of clinical trials fail to recruit enough patients during the initial recruitment period [3]

40%

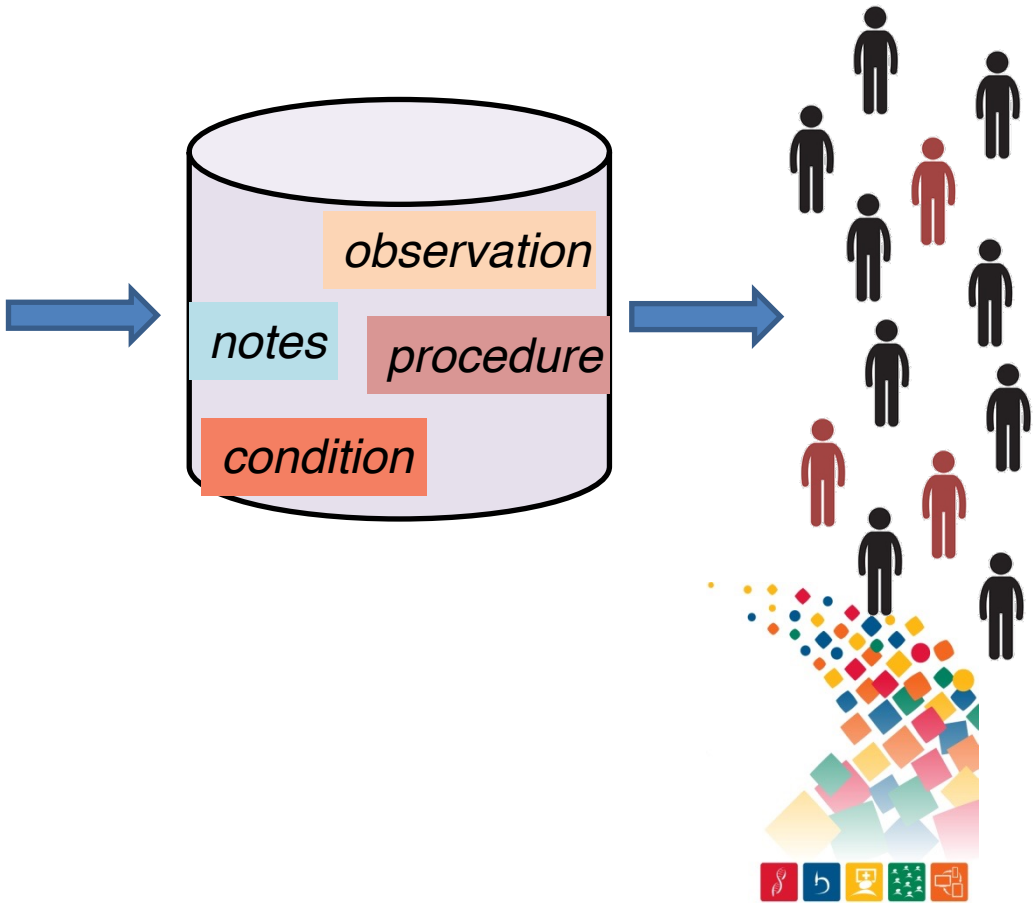
patient dropout rate in longitudinal trials

2. Sertkaya, A., et al., Examination of Clinical Trial Costs and Barriers for Drug Development. 2014, U.S. Department of Health and Human Services.
3. Sully, B.G., S.A. Julious, and J. Nicholl, A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. Trials, 2013. 14: p. 166.
4.The Expanding Web of Clinical Trial Patient Recruitment. 2014.

Eligibility E-screening

- Clinical diagnosis of ST-segment elevation acute myocardial infarction
- Must be treated within 12 hours after symptom onset
- Must be able to walk
- Must receive successful primary percutaneous coronary intervention

NCT01484158



Related Work

i2b2

TriNetX

ATLAS

TrialX

Physio-MIMI

VISAGE

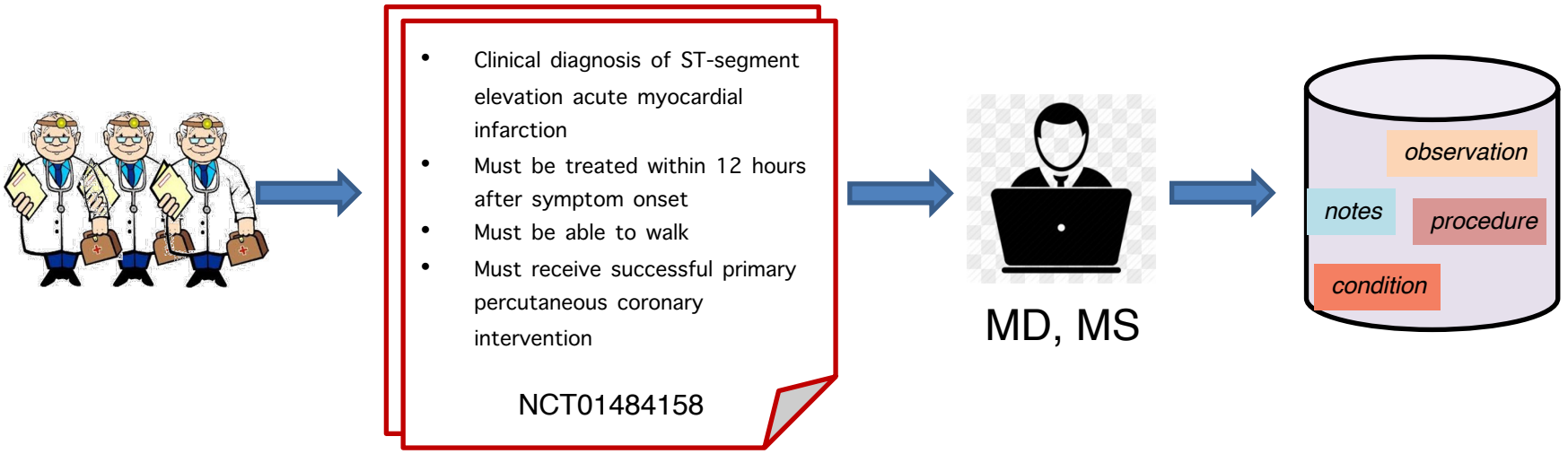
LEAF

ACT

Recruitment Innovation Center

…many other research prototypes

The real world practice



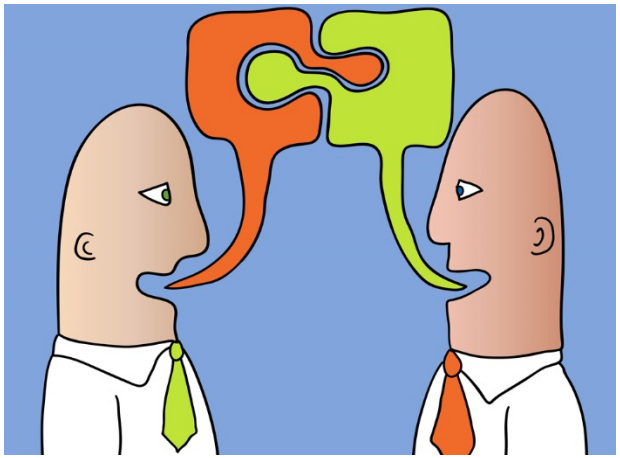
- *High cost*
- *Long waiting time & **no autonomy** for clinician research staff*
- *Fragmented knowledge*
- *Limited query reuse and knowledge sharing*
- *Variability in resulting queries*

Query Clarification

"Diseases that compromise respiratory function"

ICD 10 = J45.9
ICD 10 = J44.9
ICD 10 = J43.9
…..
(*: a list of conditions such as Asthma, COPD, lung cancer, etc.)

VERY DIFFICULT



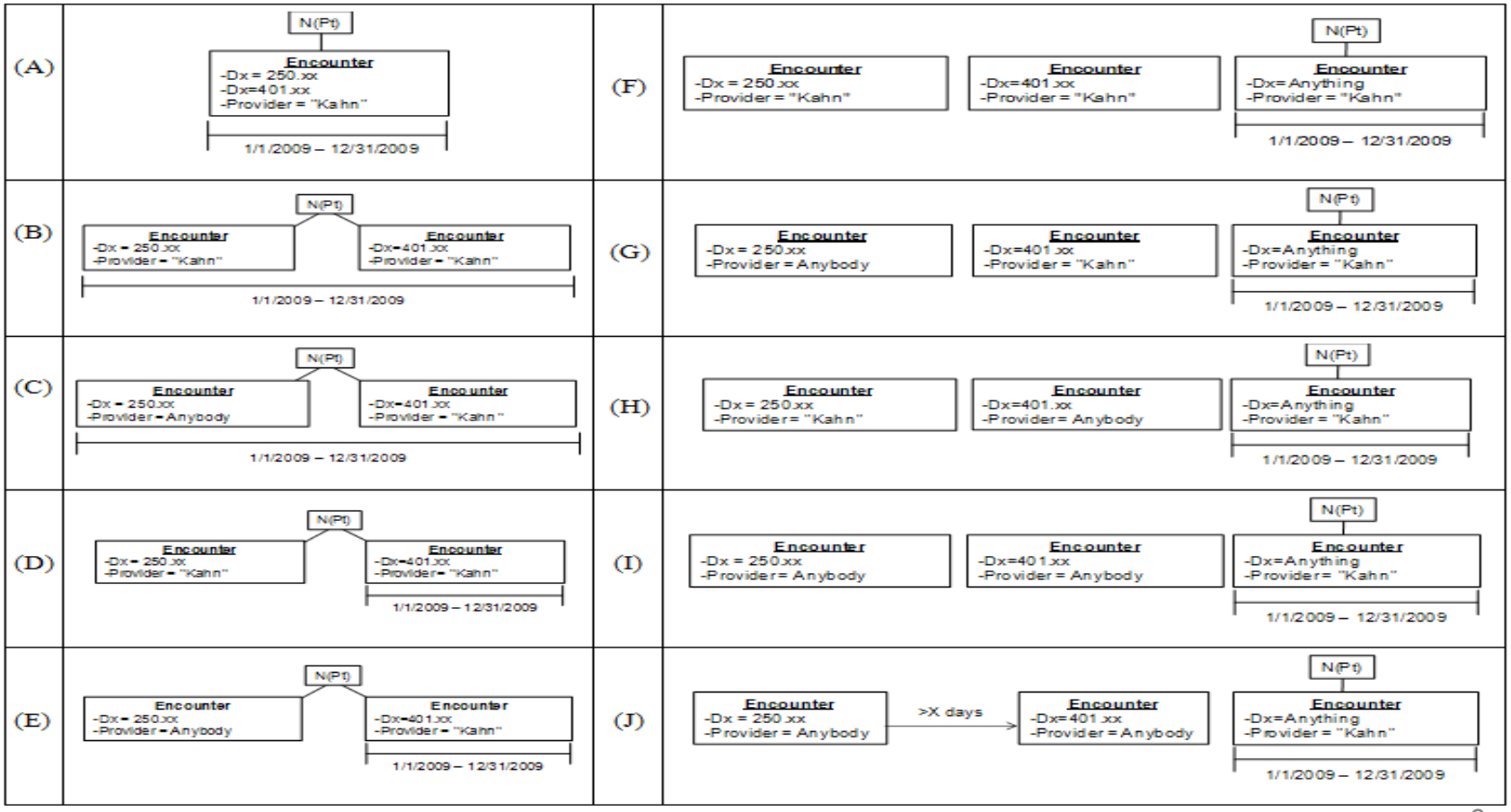
Medical Researcher

Query Analyst

Ten Translations for One Criterion

e.g., "*ambulatory patients seen by Dr. Michael Kahn with diabetes mellitus and essential hypertension between 1/1/2009 and 12/31/2009?*"

Table 1: Ten graphical diagrams representing the question: "How many ambulatory patients did I ("Provider = Kahn") see with diabetes mellitus (ICD-9 = 250.xx) and essential hypertension (ICD-9 = 401.xx) between January 1, 2009 and December 31, 2009?" Each diagram, when converted into a database query, returns a different result. N(Pt) = number of patients.



Michael.Kahn@childrenscolorado.org

E-screening is more than database querying…

AMIA
INFORMATICS PROFESSIONALS. LEADING THE WAY.

JAMIA
A SCHOLARLY JOURNAL OF INFORMATICS IN HEALTH AND BIOMEDICINE

What researchers/coordinators need

1. Criteria Prioritization

AMIA Annu Symp Proc. 2015; 2015: 2025–2034.
Published online 2015 Nov 5.
PMCID: PMC4765677
PMID: 26958302

Desiderata for Major Eligibility Criteria in Breast Cancer Clinical Trials

Matthew L. Paulson, MPH and Chunhua Weng, PhD

Author information · Copyright and License information Disclaimer

Abstract Go to:

Use of major eligibility criteria is a popular but unstudied folk practice for improving patient screening efficiency for clinical studies. This mixed-methods research study derived the desiderata for major eligibility criteria in breast cancer clinical trials. We randomly selected thirty interventional breast cancer clinical trials conducted at The New York-Presbyterian Hospital on the Columbia University Medical Center campus to create training (N=20) and testing (N=10) datasets. We utilized the Think-aloud protocol

Minor vs. Major Eligibility Criteria

- Rare phenomena are minor
  - *"I would call that minor…the majority of the population is not HIV-positive"*
  - *"The things that are less common become in my mind not major"*

- Disease staging is major
  - *"So, the disease staging, I would consider major. That's your number one."*
  - *"Staging, this is probably one of the most major, most important"*

Paulson M, Weng C, Desiderata for Major Eligibility Criteria in Breast Cancer Trials, *AMIA Annu Symp Proc. 2015 Nov 5;2015:2025-34.*

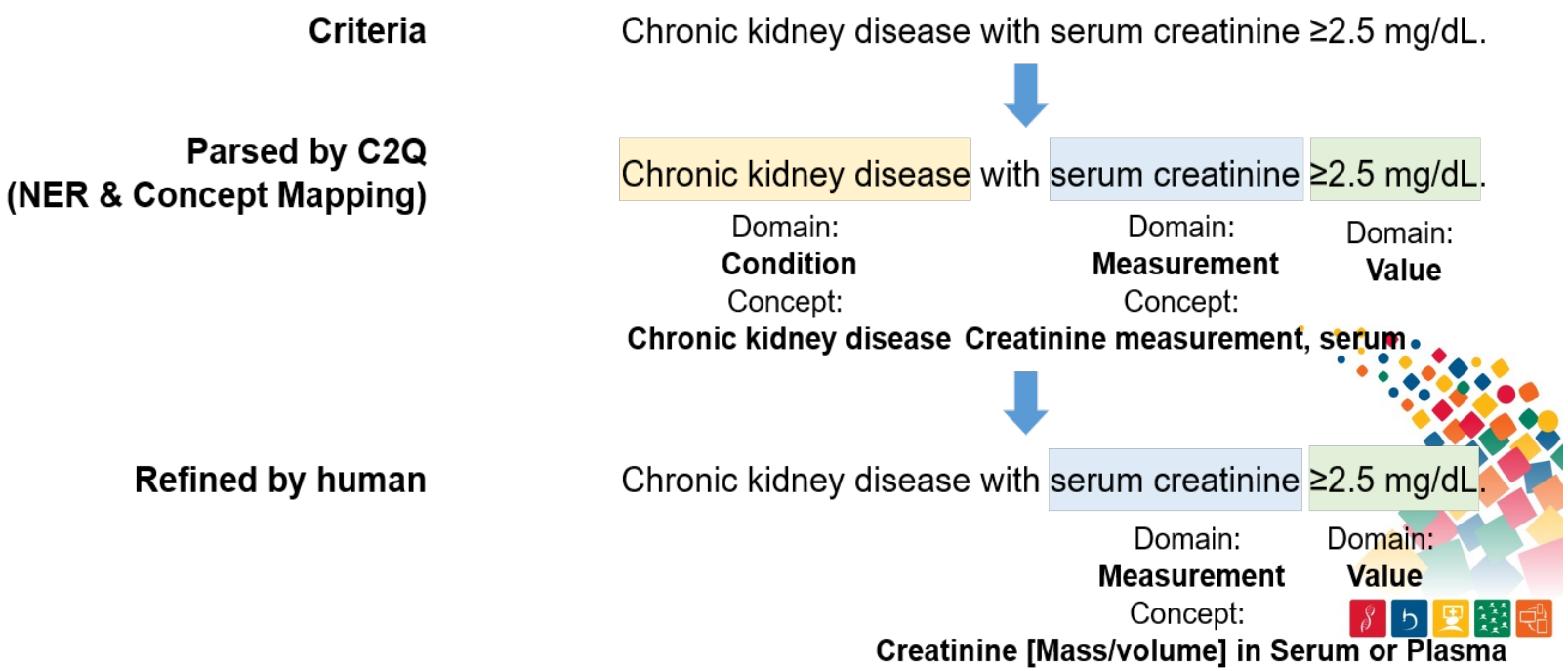
Contextual Major Eligibility Criteria

- Age
  - *"…most of the patients that we see are over 18, so that's usually an assumption I make…"*
  - *"When the cut off is larger, like 50, it's when I would consider it more of a major (criterion)"*
- Laboratory results
  - Study Coordinator: *"I can assess the labs…so that's a major to me"*
  - Nurse: *"let's say the patient is essentially eligible except for some lab variations, for the most part in my experience, this can be remedied"*

Paulson M, Weng C, Desiderata for Major Eligibility Criteria in Breast Cancer Trials, *AMIA Annu Symp Proc. 2015 Nov 5;2015:2025-34.*

What researchers/coordinators need

1. *Criteria Prioritization*
2. Criteria Simplification



Example simplification

- Removal of explanatory text
- Removal of redundant details
- Removal of subjective criteria
- Removal of vague, non-specific criteria

Example Simplification at sentence level

Omit from queries:

- Information about research activity authorization
  - E.g., "*Additional cardiac imaging, such as cardiac MRI, or cardiac CT will be performed at the discretion of the local treating physician and PI*"
- Criteria requiring further patient inquiry or a principal investigator's discretion
  - E.g., whether the female or male are sexually active or whether the female is post-menopausal may not be documented in clinical data and hence need further inquiry.
- Criteria regarding informed consent or willingness for protocol compliance
  - E.g., "*Inability of either participant or surrogate to provide written, informed consent for participation*"

Example Simplification at phrase level

Discard from queries:

- Imaging results for ruling out a certain condition
  - E.g., "*clinical diagnosis of ischemic stroke and brain imaging to rule out hemorrhagic stroke*": since it contains "*hemorrhagic stroke*" condition, the imaging procedure is not critically needed.
- Broad and unspecified concepts
  - E.g., "*No major-risk cardioembolic source of embolism, including intracardiac thrombus, mechanical prosthetic cardiac valve…*": "*major-risk cardioembolic source of embolism*" term can be ignored, but we should still include their examples.
- General disease conditions followed by more specific measurements to define them.
  - E.g., "*chronic kidney disease with serum creatinine ≥ 2.5 mg/dL*" contains "*chronic kidney disease*" condition and its relevant measurement "serum creatinine".
- Measurements without their explicit or implicit value thresholds
  - E.g., all measurements without value have been removed from the final simplified cohort query.

Public Health and Informatics
J. Mantas et al. (Eds.)

doi:10.3233/SHTI210325

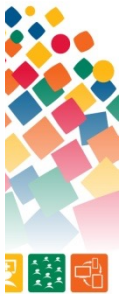
Participatory Design of a Clinical Trial Eligibility Criteria Simplification Method

Yilu FANG[a], Jae Hyun KIM[a], Betina Ross IDNAY[b,c], Rebeca ARAGON GARCIA[c], Carmen E. CASTILLO[c], Yingcheng SUN[a], Hao LIU[a], Cong LIU[a], Chi YUAN[a] and Chunhua WENG[a,1]

[a] *Department of Biomedical Informatics*
[b] *School of Nursing*
[c] *Department of Neurology, Columbia University, New York, NY, USA*

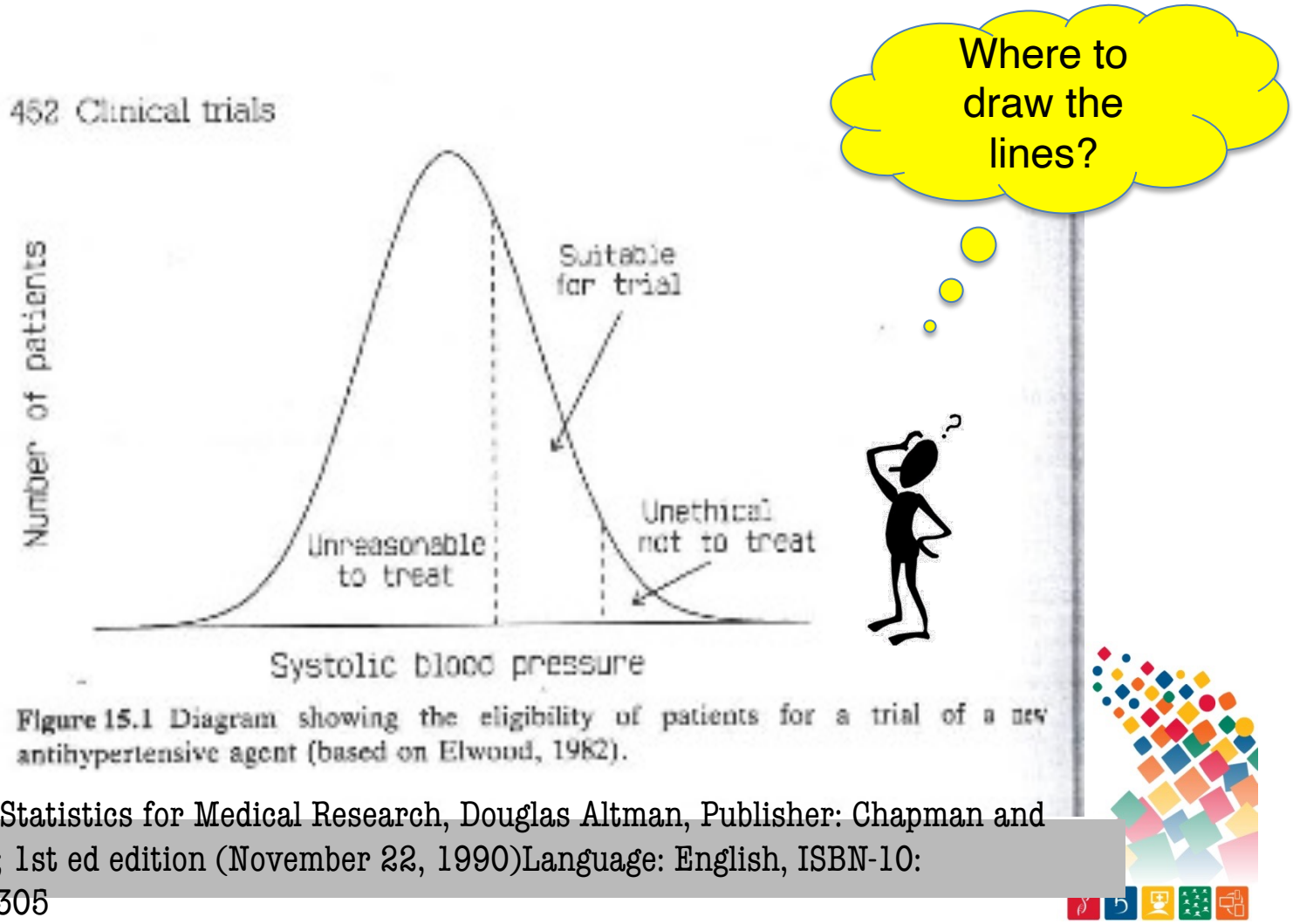
Abstract. Clinical trial eligibility criteria are important for selecting the right participants for clinical trials. However, they are often complex and not computable. This paper presents the participatory design of a human-computer collaboration method for criteria simplification that includes natural language processing followed by user-centered eligibility criteria simplification. A case study on the ARCADIA trial shows how criteria were simplified for structured database querying by clinical researchers and identifies rules for criteria simplification and concept normalization.

Keywords. named entity recognition, concept mapping, intelligence augmentation



What researchers/coordinators need

1. *Criteria Prioritization*
2. *Criteria Simplification*
3. Criteria Optimization



Practical Statistics for Medical Research, Douglas Altman, Publisher: Chapman and Hall/CRC; 1st ed edition (November 22, 1990)Language: English, ISBN-10: 0412276305

The electronic health records data could be utilized to optimize the inclusion criteria for clinical trials

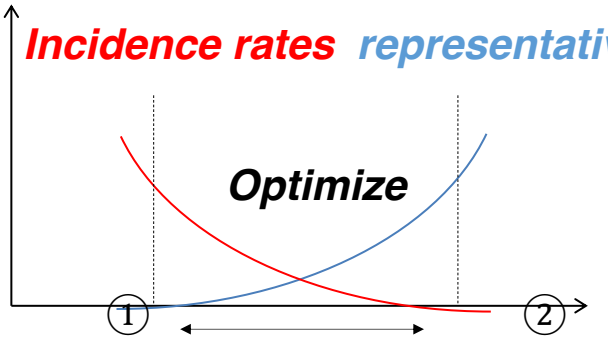
Empirical list of inclusion criteria

- Myocardial infarction
- Stroke
- Coronary artery stenosis
- Coronary revascularization
- Peripheral arterial disease
- On antihypertensive agents
- On lipid-lowering agents
- Current smoker
- Albuminuria
- …

EHR

Calculate
- Representativeness
- Incidence rates

"Optimized" list of inclusion criteria for different scenario



① criteria with highest incidence rate

…

② criteria with highest representativenes

Journal of the American Medical Informatics Association, 28(1), 2021, 14–22
doi: 10.1093/jamia/ocaa276
Advance Access Publication Date: 1 December 2020
Research and Applications

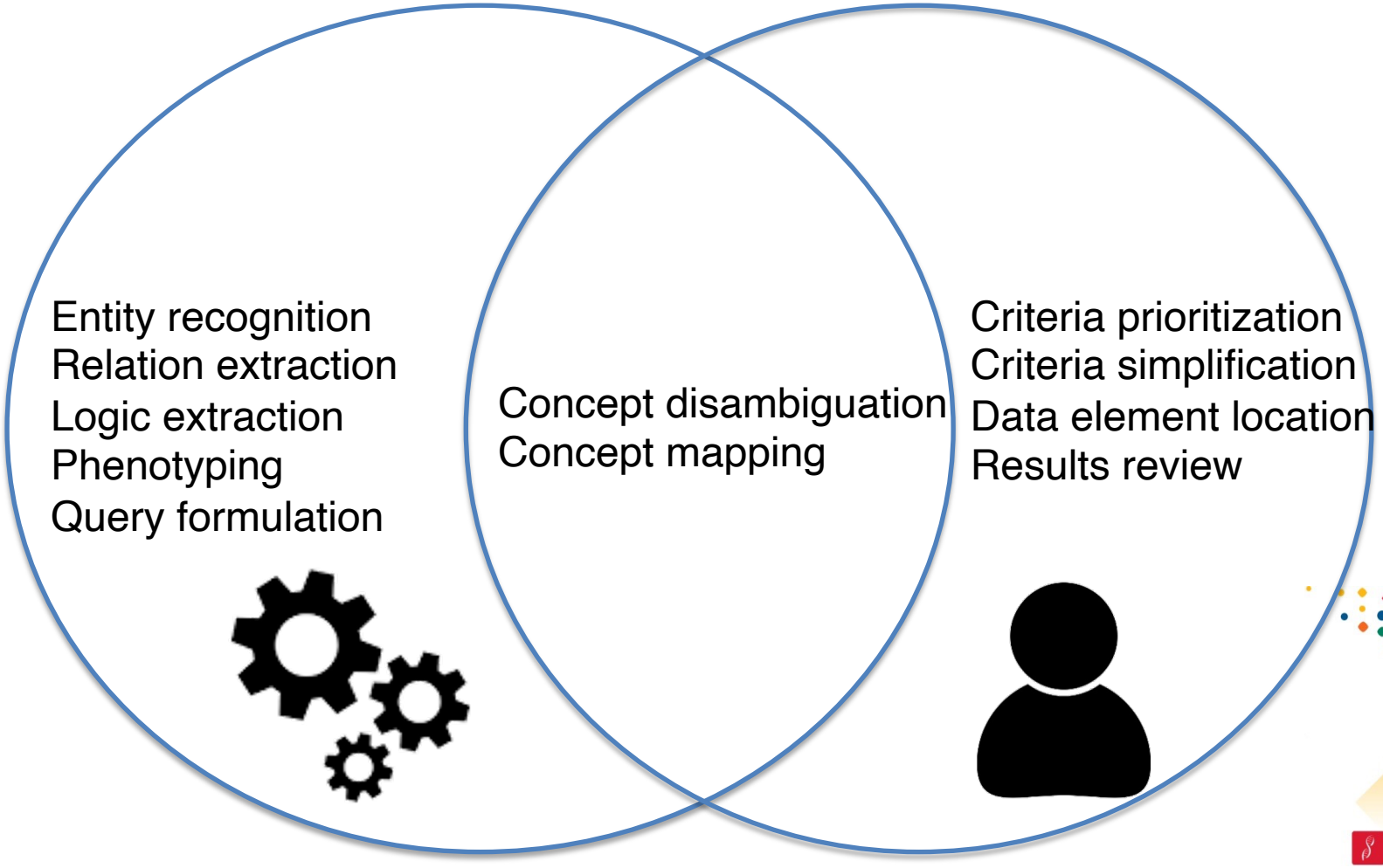
Research and Applications

Towards clinical data-driven eligibility criteria optimization for interventional COVID-19 clinical trials

Jae Hyun Kim,[1] Casey N. Ta,[1] Cong Liu,[1] Cynthia Sung,[2] Alex M. Butler,[1] Latoya A. Stewart,[1] Lyudmila Ena,[1] James R. Rogers,[1] Junghwan Lee,[1] Anna Ostropolets,[1] Patrick B. Ryan,[1,3,4] Hao Liu,[1] Shing M. Lee,[5] Mitchell S.V. Elkind,[6,7] and Chunhua Weng[1]

[1]Department of Biomedical Informatics, Columbia University, New York, New York, USA, [2]Health Services and Systems Research, Duke-NUS Medical School, Singapore, [3]Observational Health Data Sciences and Informatics, New York, New York, USA, [4]Epidemiology Analytics, Janssen Research and Development, Titusville, New Jersey, USA, [5]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, USA, [6]Department of Neurology, Vagelos College of Physi

Combining machine and human intelligence



Machine intelligence

1. **Entity recognition**: what is being searched for?
2. **Concept disambiguation/specification**: what does it mean here?
3. **Concept mapping**: how is it coded in a database?
4. **Relation extraction**: which value threshold and time frame are the entities associated with?
5. **Logic extraction**: are the criteria and entities connected with "OR" or "AND"? Are the criteria and entities negated?
6. **Phenotyping**: e.g., Type 2 Diabetes, CKD, and many other e-phenotypes in PheKB
7. **Query formulation**: formulate queries in MS SQL, MSSQL, JSON, and other formats automatically

- Clinical diagnosis of ST-segment elevation acute myocardial infarction
- Must be treated within 12 hours after symptom onset
- Must be able to walk
- Must receive successful primary percutaneous coronary intervention

NCT01484158

Human intelligence

1. **Concept disambiguation/specification**: e.g., "diseases that affect lung function", "clinically significant infectious diseases"
2. **Concept granularity selection**: e.g., "Essential Hypertension", "Controlled Hypertension", etc.
3. **Criteria prioritization**: which major criteria should be prioritized when screening using EHR data?
4. **Criteria simplification**: which criteria can be omitted to include more patients?
5. **Entity recognition correction**: is there any error in NLP results (after all, NLP is not perfect)?
6. **Data element location**: is it in the database? If yes, where? Which source (notes vs. structured) is more reliable or convenient/cost-effectiveness?

- known history of brain injuries
- Insufficient German language skills
- evidence of Non-AD neurodegenerative disorder (e.g. Parkinson)
- contraindication to acitretin such as osteoporosis, hypoalbuminaemia

NCT01078168

Criteria2Query: a natural language interface to clinical databases for cohort definition

Chi Yuan, Patrick B Ryan, Casey Ta, Yixuan Guo, Ziran Li, Jill Hardin, Rupa Makadia, Peng Jin, Ning Shang, Tian Kang, Chunhua Weng

Journal of the American Medical Informatics Association, ocy178, https://doi.org/10.1093/jamia/ocy178
Published: 07 February 2019 **Article history** ▾

Abstract

Objective

Cohort definition is a bottleneck for conducting clinical research and depends on subjective decisions by domain experts. Data-driven cohort definition is appealing but requires

Journal of the American Medical Informatics Association, 29(7), 2022, 1161–1171
https://doi.org/10.1093/jamia/ocac051
Advance Access Publication Date: 15 April 2022
Research and Applications

Research and Applications

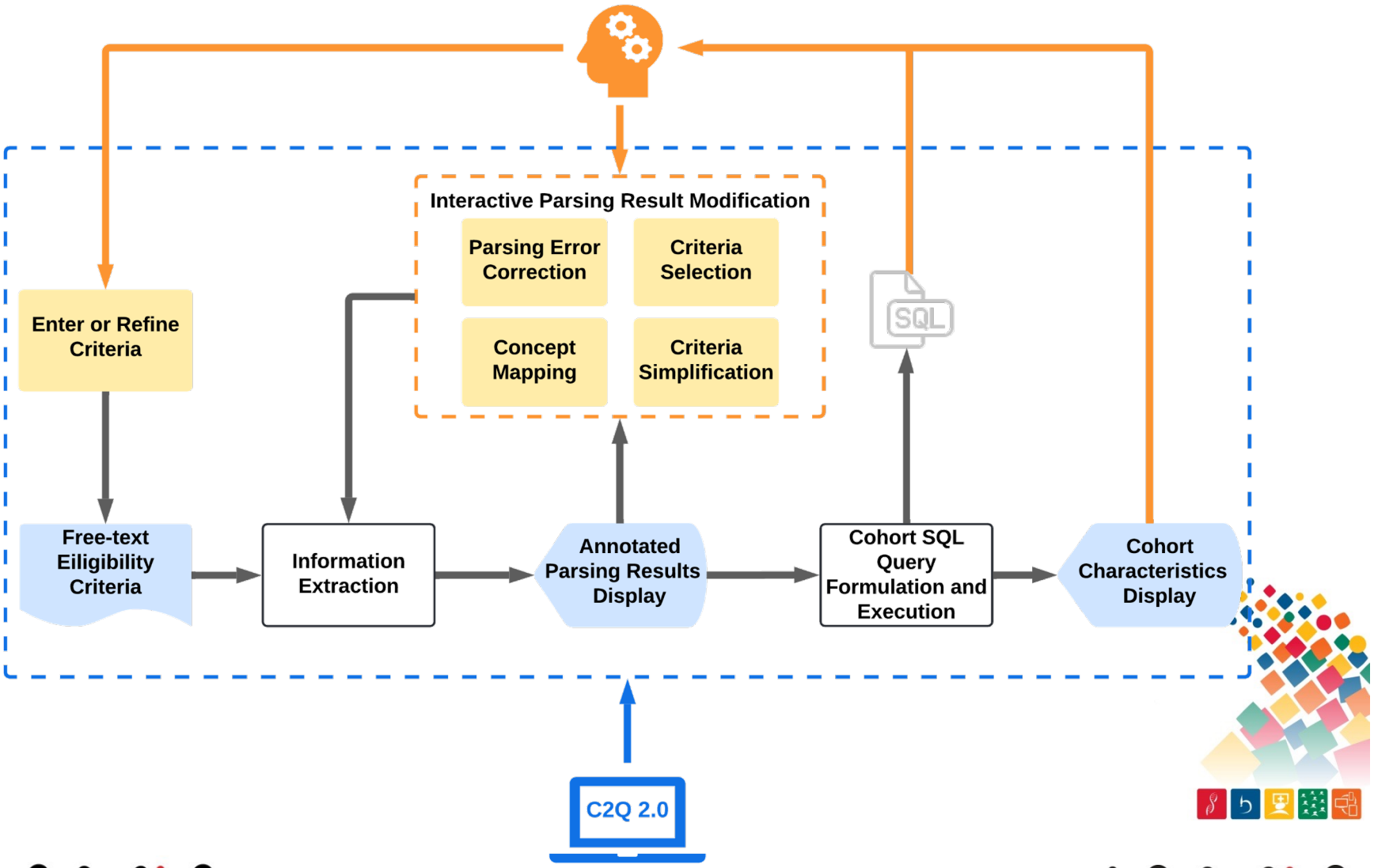
Combining human and machine intelligence for clinical trial eligibility querying

Yilu Fang [1], Betina Idnay [2,3], Yingcheng Sun [1], Hao Liu [1], Zhehuan Chen [1], Karen Marder [3], Hua Xu [4], Rebecca Schnall [2,5], and Chunhua Weng [1]

[1]Department of Biomedical Informatics, Columbia University, New York, New York, USA, [2]School of Nursing, Columbia University, New York, New York, USA, [3]Department of Neurology, Columbia University, New York, New York, USA, [4]School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, Texas, USA, and [5]Heilbrunn Department of Population and Family Health, Mailman School of Public Health, Columbia University, New York, New York, USA

Yilu Fang and Betina Idnay contributed equally as first authors.

Current interactive pipeline



A 2-min demo

https://www.youtube.com/watch?v=zZEiy7I-W4s

A 11-min demo

https://www.youtube.com/watch?v=LJsWgE0EZ-o

Publicly Available Training Data

- Kang T, Zhang S, Tang Y, Hruby GW, Rusanov A, Elhadad N, Weng C. **EliIE: An open-source information extraction system for clinical trial eligibility criteria**. J Am Med Inform Assoc. 2017 Nov 1;24(6):1062-1071. doi: 10.1093/jamia/ocx019. PMID: 28379377; PMCID: PMC6259668.

- Kury F, Butler A, Yuan C, Fu LH, Sun Y, Liu H, Sim I, Carini S, Weng C. **Chia, a large annotated corpus of clinical trial eligibility criteria**. Sci Data. 2020 Aug 27;7(1):281. doi: 10.1038/s41597-020-00620-0. PMID: 32855408; PMCID: PMC7452886.

Comparison of CHIA to related work

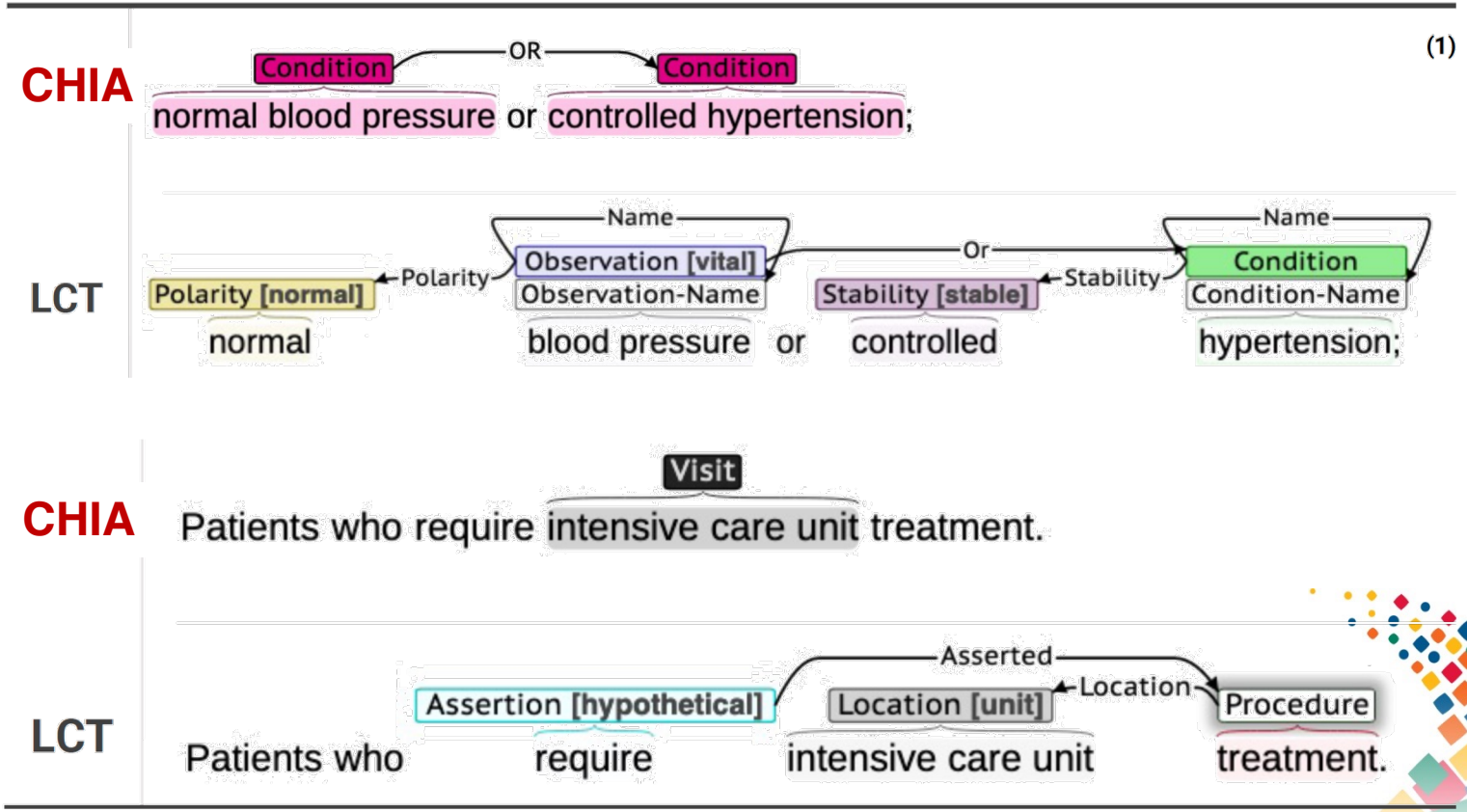
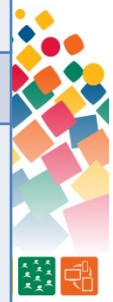


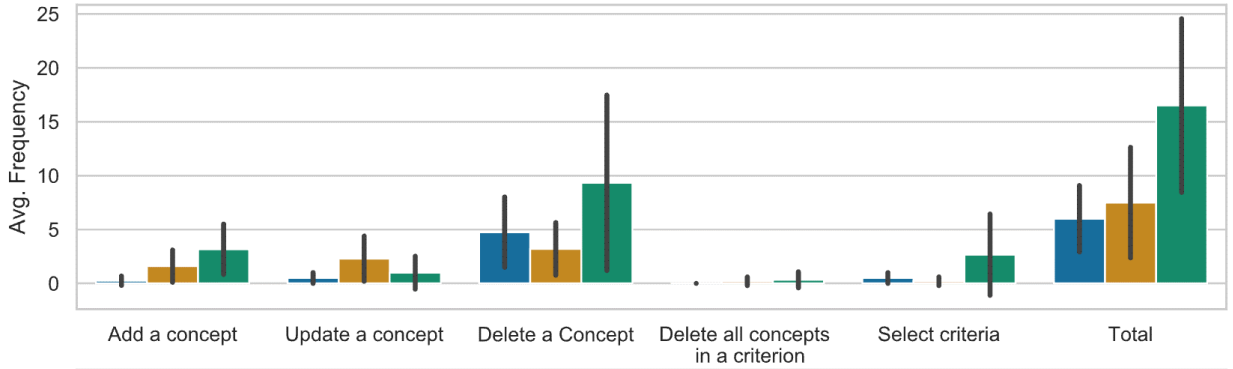
Image source: https://arxiv.org/abs/2207.13757

User evaluation – evaluator characteristics

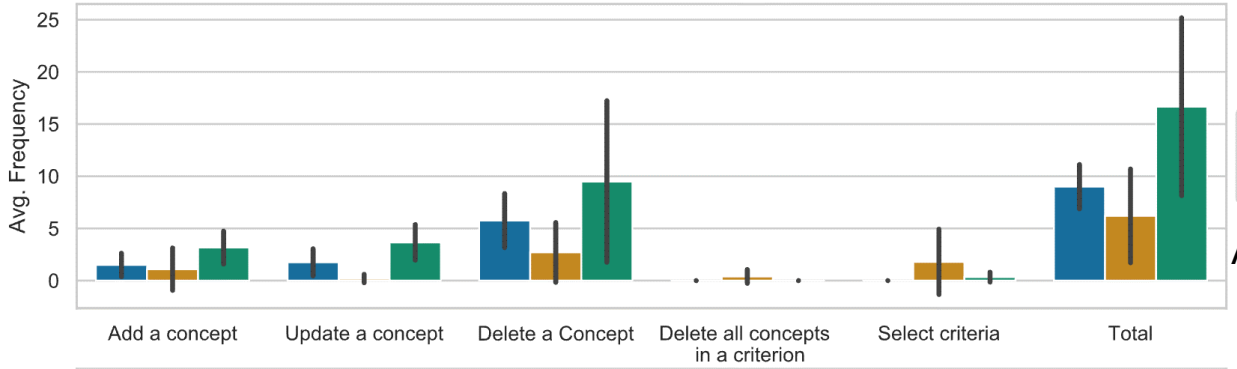
Characteristic	Category	Ten (n=10) Included Evaluators (%)
Number of years working in clinical research	Less than 1 year	2 (20)
	1 year to less than 5 years	5 (50)
	5 years or over	3 (30)
Alzheimer's disease clinical research experience	No experience	2 (20)
	Less than 1 year	5 (50)
	1 year or more	3 (30)
Involvement in prescreening potential participants for research	No	5 (50)
	Yes	5 (50)



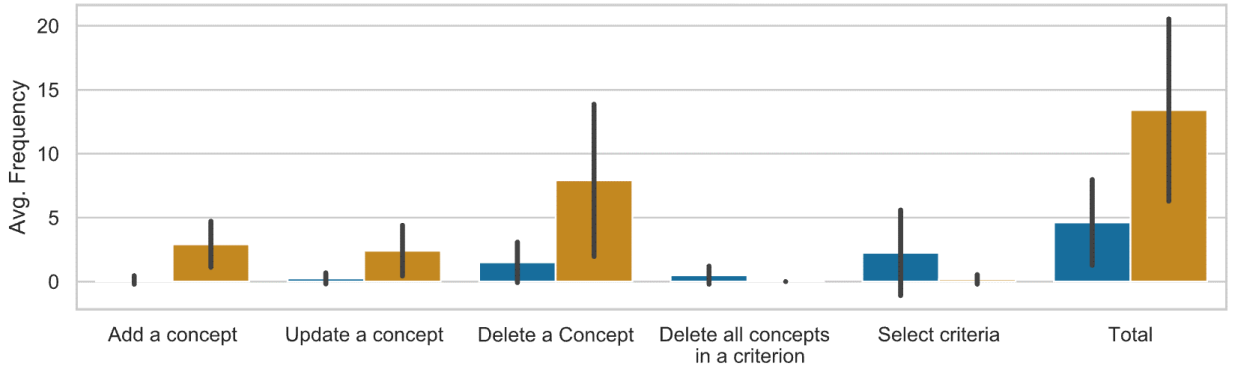
User evaluation – modification functions' usage frequency



Number of years working in clinical research



Alzheimer's disease clinical research experience



Prescreening involvement

On average, the eligibility criteria parsing result received 9.9 modifications per clinical trial. Concept deletion was the most frequently used function. Besides, evaluators with a longer clinical research experience, at least one year of research experience in AD, or prescreening experience, made more modifications.

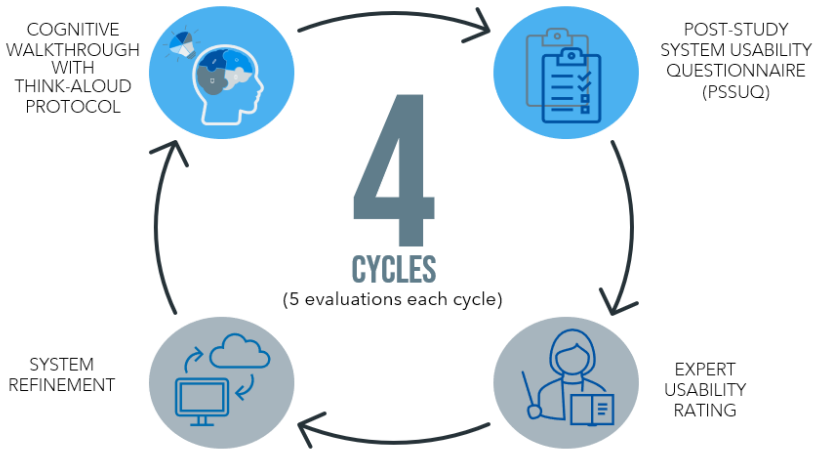
User evaluation – usability score

	Mean (SD)
Health-ITUES	
Perceived usefulness	3.99 (0.66)
Perceived ease of use	3.80 (1.06)
User control	3.73 (0.89)
Overall score	**3.84 (0.71)**
Feature-specific	
Pleasant to use	3.90 (0.57)
User satisfaction: automatically generated criteria parsing result	**4.00 (0.67)**
User satisfaction: modified criteria parsing result	**4.10 (0.74)**
Easy to learn: add a concept	4.50 (0.53)
Easy to learn: update a concept	4.70 (0.49)
Easy to learn: delete a concept	4.60 (0.52)
Easy to learn: delete all concepts in an eligibility criterion	4.60 (0.52)
Easy to learn: select eligibility criteria	4.30 (0.95)
Availability of all user engagement features	**4.30 (0.95)**

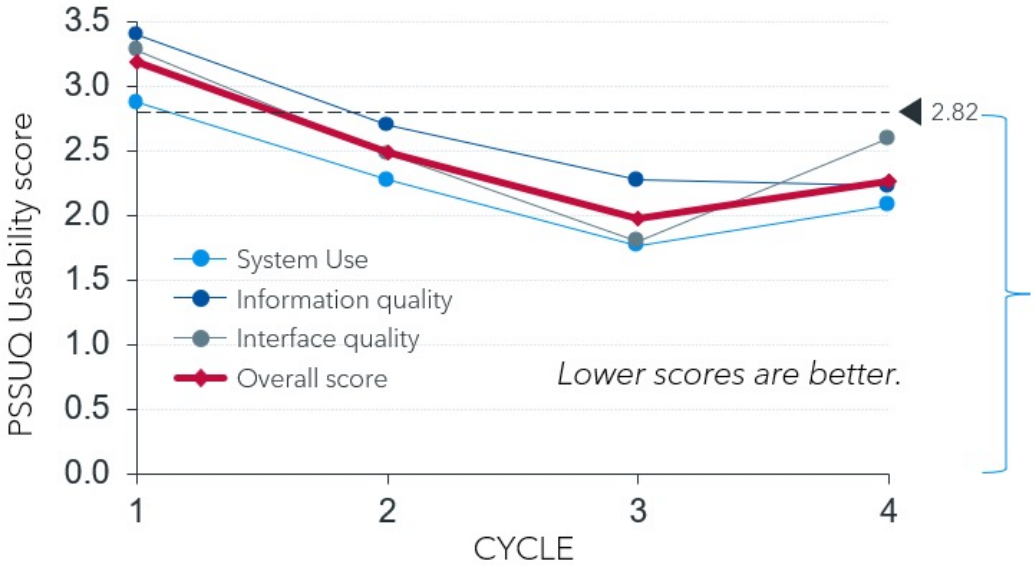
Open-ended feedback from coordinators

- Comments:
  - "***straightforward***"
  - "***easy*** *to understand and use.*"
  - "*This is a wonderful tool that is very* ***effective*** *at extracting and mapping criteria from clinical trials.*"
  - "*I* ***wanted to exclude whole paragraphs*** *from the parsing where I was pessimistic that the parsing could actually capture what the intention behind the criterion was.*"
- Recommendations:
  - "*allow to edit the automated inclusion and exclusion criteria to add a new criterion.*"
  - "*instead of using keys to edit maybe have dropdowns*" and "*adding a bit more instructions would be useful*."

Iterative usability evaluation using Cognitive Walkthrough



C2Q achieved high usability after the first cycle.



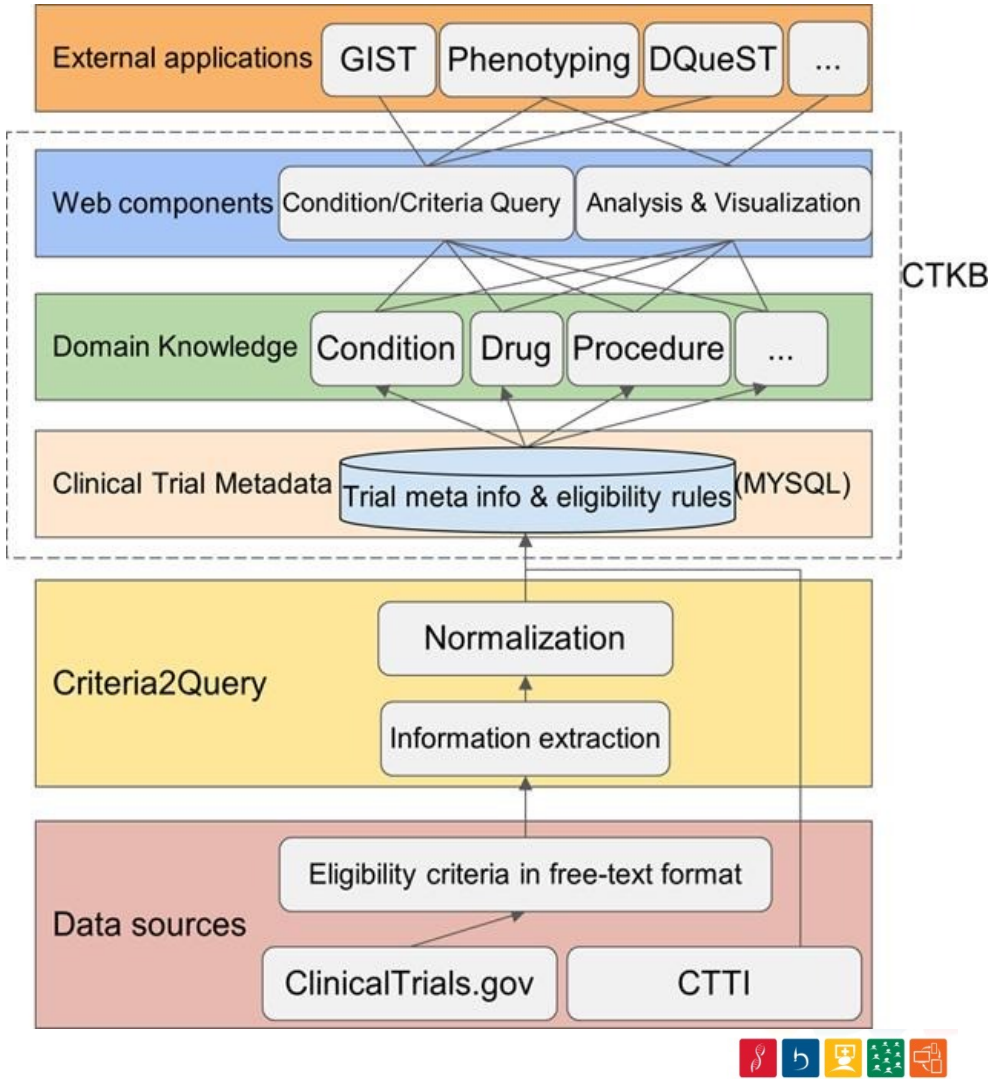
Betina Idnay, MPH

Limitations & Future work

- *"Adults" → "age >= 21"*
- *Linkage to phenotyping algorithm repositories*
- *Linkage to CTKB*
- *"Human in the loop" active learning*
  - *PRIORITIZATION*
  - *SIMPLIFICATION*
  - *CONCEPT MAPPING*
  - *etc.*
- *Empowering researchers with informatics skills*
- *Tradeoff between technology complexity and usability*

Clinical **T**rial **K**nowledge **B**ase (**CTKB**)

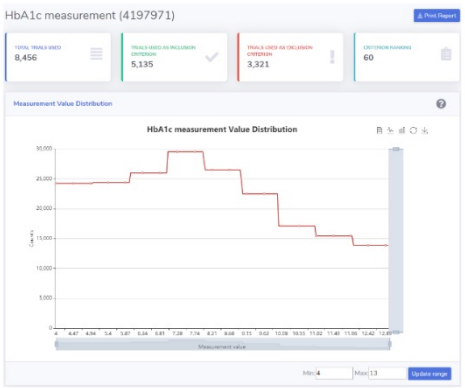
http://ctkb.io



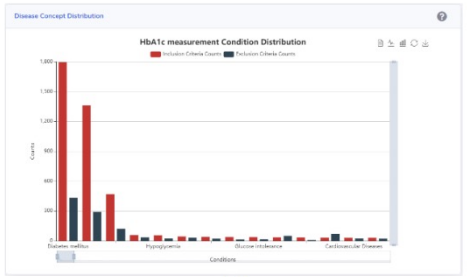
Liu H, Yuan C, Butler A, Sun Y, Weng C. A knowledge base of clinical trial eligibility criteria. J Biomed Inform. 2021 May;117:103771. doi: 10.1016/j.jbi.2021.103771. Epub 2021 Apr 1. PMID: 33813032; PMCID: PMC8407851.

CTKB use case (I - Criteria Summary)

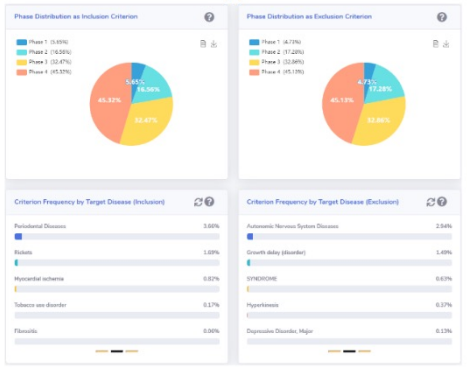
- **A criterion's usage frequency** among all clinical trials, including: its frequency used as inclusion criterion, exclusion criterion, and its rank among all criteria in our knowledge base (Figure (a));
- **Disease Concept Distribution section** (Figure (b)). This section shows the counts of a criterion used as inclusion criterion (red bar) and exclusion criterion (black bar) binned by target disease.
- **Phase Distribution** of a criterion (Figure (c)) used as inclusion criteria and exclusion criteria.



(a)

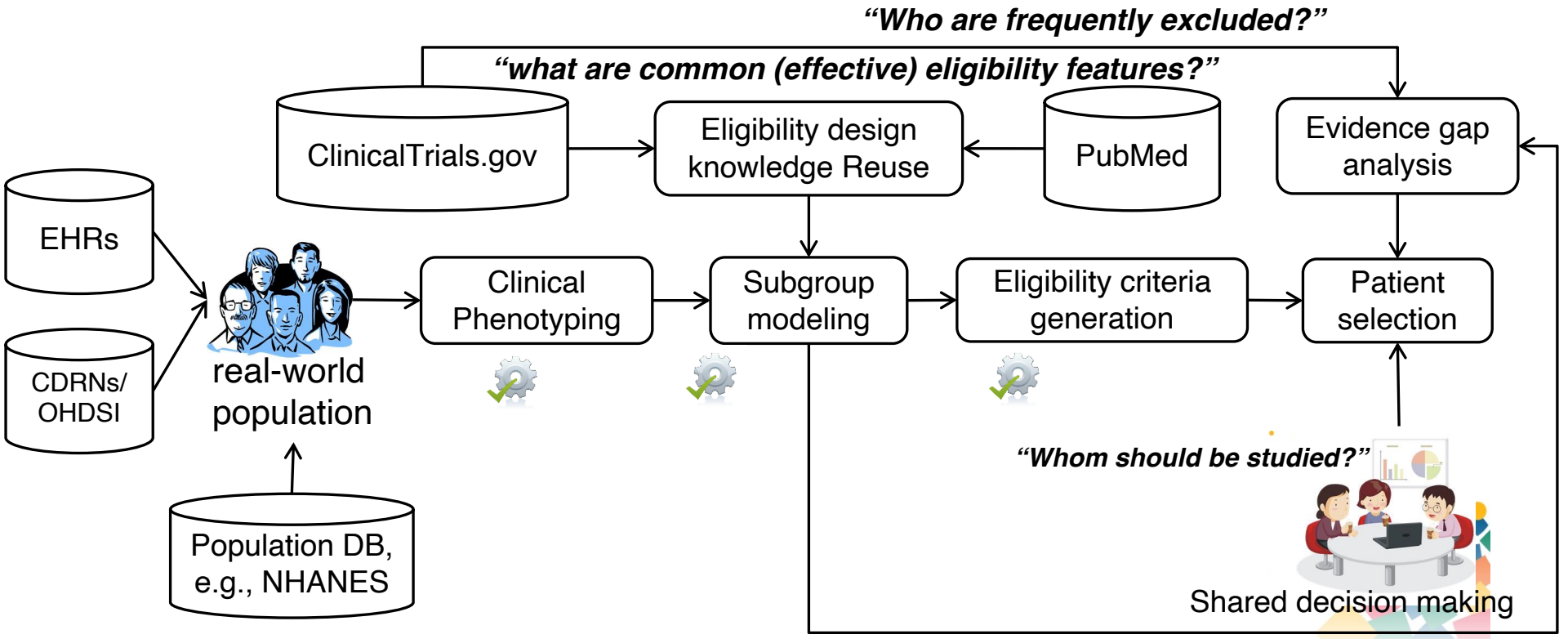


(b)



(c)

Knowledge-based and Data-driven Optimization of Eligibility Criteria Design



Weng C, Optimizing Clinical Research Participant Selection with Informatics, *Trends in Pharmacological Sciences* 36 (2015), Cell Press, pp. 706-709.

Key Takeaways

E-screening is more than database querying…

not only about precision, recall, F-measure, but also about what matters to researchers

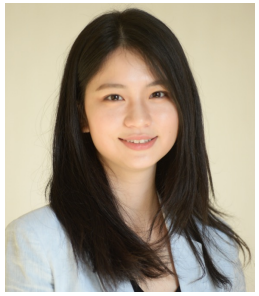
"can I use the tool myself?"
"can I incorporate my knowledge?"

Acknowledgments

R01LM009886 (2009-present):
Bridging the semantic gap between research criteria and clinical data


Yilu Fang, MA


Betina Idnay, MPH


Tian Kang, PhD


Chi Yuan, PhD


Cong Liu, PhD


Hao Liu, PhD


Patrick Ryan, PhD


Alex Butler, MD


James Rogers, PhD


Casey Ta, PhD


Jaehyun Kim, PharmD


Yingcheng Sun, PhD

Thank you!

chunhua@columbia.edu