Challenges of Clinical Trial Patient Recruitment

- $900,000 on average spent on patient recruitment and retention [3]
- 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 [5]
- 40% patient dropout rate in longitudinal trials

References:
- The Expanding Web of Clinical Trial Patient Recruitment. 2014.

https://www.azenta.com/blog/solving-patient-recruitment-challenges-sample-repurposing
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

ACT

VISAGE

LEAF

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

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
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.
E-screening is more than database querying...
What researchers/coordinators need

1. Criteria Prioritization

Desiderata for Major Eligibility Criteria in Breast Cancer Clinical Trials

Matthew L. Paulson, MPH and Chunhua Weng, PhD

Abstract

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”

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”

What researchers/coordinators need

1. Criteria Prioritization

2. Criteria Simplification

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Chronic kidney disease with serum creatinine ≥2.5 mg/dL.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsed by C2Q (NER &amp; Concept Mapping)</td>
<td>Chronic kidney disease with serum creatinine ≥2.5 mg/dL.</td>
</tr>
<tr>
<td>Refined by human</td>
<td>Chronic kidney disease with serum creatinine ≥2.5 mg/dL.</td>
</tr>
</tbody>
</table>

Domain: Condition
Concept: Chronic kidney disease

Domain: Measurement
Concept: Creatinine measurement, serum

Domain: Value

Creatinine [Mass/volume] in Serum or Plasma
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

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

- **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.
Participatory Design of a Clinical Trial Eligibility Criteria Simplification Method

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

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
Where to draw the lines?

Figure 15.1 Diagram showing the eligibility of patients for a trial of a new antihypertensive agent (based on Elwood, 1982).

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
- ...

### "Optimized" list of inclusion criteria for different scenarios

- **Calculate**
  - Representativeness
  - Incidence rates

- **Optimize**
  - ① criteria with highest incidence rate
  - ② criteria with highest representativeness

*Incidence rates* representativeness
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 Weng1

1Department of Biomedical Informatics, Columbia University, New York, New York, USA, 2Health Services and Systems Research, Duke-NUS Medical School, Singapore, 3Observational Health Data Sciences and Informatics, New York, New York, USA, 4Epidemiology Analytics, Janssen Research and Development, Titusville, New Jersey, USA, 5Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, USA, 6Department of Nuclear Medicine, College of Physicians
Combining machine and human intelligence

- Entity recognition
- Relation extraction
- Logic extraction
- Phenotyping
- Query formulation

- Concept disambiguation
- Concept mapping

- Criteria prioritization
- Criteria simplification
- Data element location
- Results review
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


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

https://doi.org/10.1093/jamia/ocy178
Research and Applications

Combining human and machine intelligence for clinical trial eligibility querying

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

\textsuperscript{1}Department of Biomedical Informatics, Columbia University, New York, New York, USA, \textsuperscript{2}School of Nursing, Columbia University, New York, New York, USA, \textsuperscript{3}Department of Neurology, Columbia University, New York, New York, USA, \textsuperscript{4}School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, Texas, USA, and \textsuperscript{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.

\url{https://doi.org/10.1093/jamia/ocy178}
Current interactive pipeline

- Enter or Refine Criteria
- Free-text Eligibility Criteria
- Information Extraction
- Annotated Parsing Results Display
- Cohort SQL Query Formulation and Execution
- Cohort Characteristics Display

Interactive Parsing Result Modification
- Parsing Error Correction
- Criteria Selection
- Concept Mapping
- Criteria Simplification
A 2-min demo

https://www.youtube.com/watch?v=zZEiy7l-W4s

A 11-min demo

https://www.youtube.com/watch?v=LJsWgE0EZ-q
Publicly Available Training Data


Comparison of CHIA to related work

CHIA

normal blood pressure or controlled hypertension;

LCT

Polarity [normal]

normal

Observation [vital]

Observation-Name

blood pressure or controlled

Stability [stable]

Condition

Condition-Name

hypertension;

CHIA

Patients who require intensive care unit treatment.

LCT

Patients who require intensive care unit treatment.
# User evaluation – evaluator characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Ten (n=10) Included Evaluators (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of years working in clinical research</strong></td>
<td>Less than 1 year</td>
<td>2 (20)</td>
</tr>
<tr>
<td></td>
<td>1 year to less than 5 years</td>
<td>5 (50)</td>
</tr>
<tr>
<td></td>
<td>5 years or over</td>
<td>3 (30)</td>
</tr>
<tr>
<td><strong>Alzheimer’s disease clinical research experience</strong></td>
<td>No experience</td>
<td>2 (20)</td>
</tr>
<tr>
<td></td>
<td>Less than 1 year</td>
<td>5 (50)</td>
</tr>
<tr>
<td></td>
<td>1 year or more</td>
<td>3 (30)</td>
</tr>
<tr>
<td><strong>Involvement in prescreening potential participants for research</strong></td>
<td>No</td>
<td>5 (50)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5 (50)</td>
</tr>
</tbody>
</table>
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

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

http://ctkb.io

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

“Who are frequently excluded?”

“what are common (effective) eligibility features?”

ClinicalTrials.gov → Eligibility design knowledge Reuse → PubMed → Evidence gap analysis

Clinical Phenotyping → Subgroup modeling → Eligibility criteria generation → Patient selection

“Whom should be studied?”

EHRs

real-world population

CDRNs/OHDSI

Population DB, e.g., NHANES

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

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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!

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