Observational Studies:

Leveraging data for Clinical Trials

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Goals

- Basic observational study designs
- How to leverage for planning a trial
- How to design them if you need more data

The Scientific Method

- Observe a phenomenon
- Develop a hypothesis that explains the observation
- Design a Test of the Hypothesis
- Experiment

Observational Studies

- Observational studies include case series, case-control, surveys, cohort studies
- Literature Review is the most common way of building data but with new electronic medical records tools, can develop some preliminary data quickly
- Observational studies or data build the foundation for most research.
- The following slides describe different types of observational studies

Observational Studies

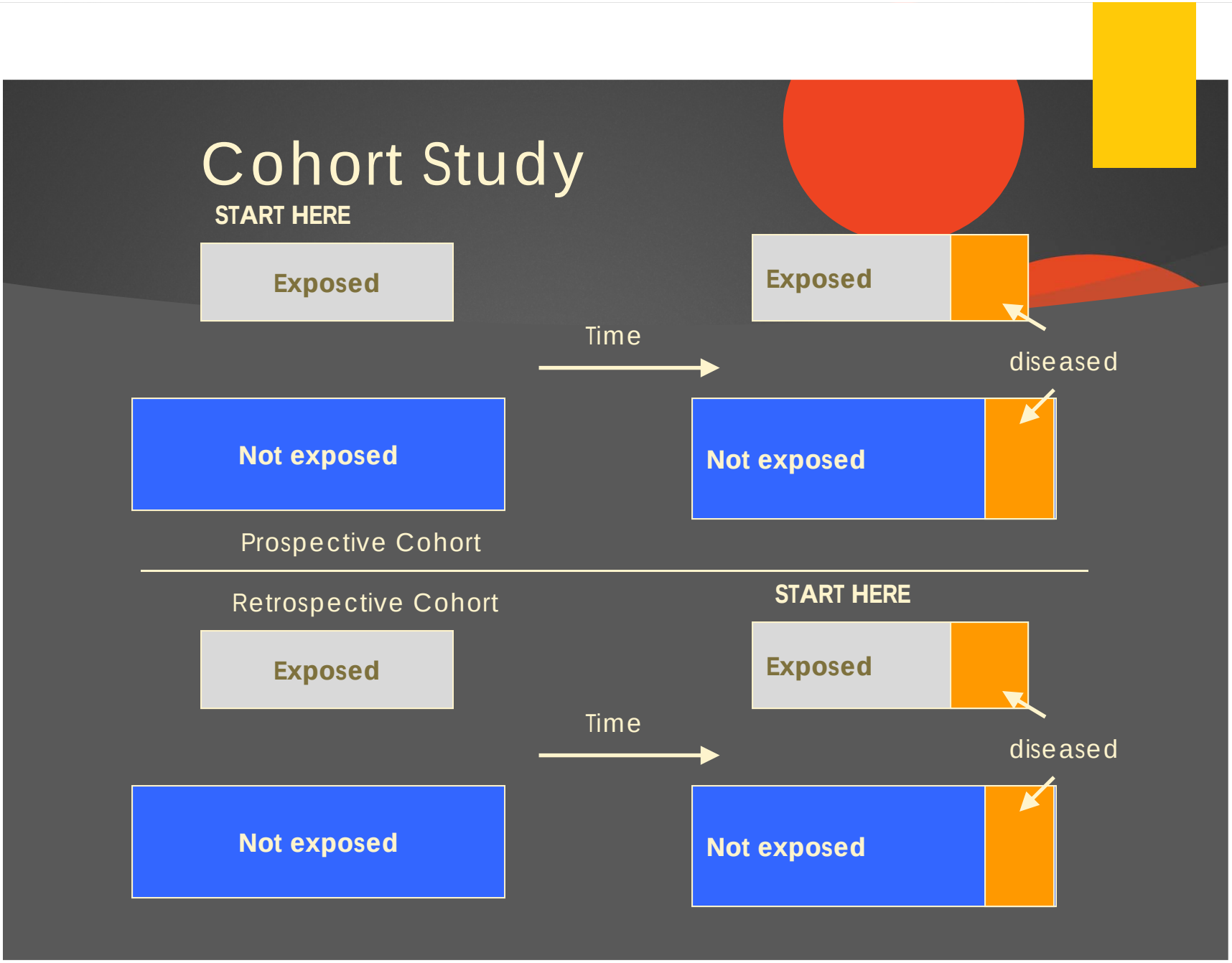
- Why isn't everything a randomized controlled trial?
- Rare event rate:
  - The annual incidence of lung cancer is 55.8 per 100,000 per year. Or, if you recruit 100,000 people, you will get 55.8 cases per year or 279 cases in 5 years.
  - Thus, to get a sample size of 1000 cases of lung cancer in 5 years, you would need to recruit 3.5*100,000 people or 350,000 people
- Unethical:
  - Why aren't their randomized trials to prove that smoking is a risk factor for lung cancer?
  - Is it ethical to randomize 350,000 people to smoking?
  - Is it ethical to randomize patients to 'untreated hypertension'?
  - And yet, in the population, some people smoke and some people have hypertension but don't take or can't afford their medicine. To test hypotheses related to these, one must perform observational studies
- Need some evidence before proceeding to trial
  - Almost all randomized trials rely on preliminary data that there is a signal of effect or a phenomenon observed that is the basis for the trial.

Observational Studies

- Case Series – Can be a single report or a series of interesting cases
- Case-control – Cases are compared to controls
- Cohort – A group of subjects are followed in which some end up as cases and the rest can be used as controls
  - Can be retrospective or prospective
- Cross-sectional studies – A single point in time along a population to identify the proportion of cases or an exposure

Cohort Studies

- Cohort: 300-600 soldiers who moved together into combat
- Some had shields and others were ‘exposed’
- Thus, the relationship of ‘exposure’ to disease’ can be determined
- Being ‘exposed’ to arrows was a high risk for injury and death


Cohort Study
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Exposed
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Prospective Cohort
Retrospective Cohort
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Cohort Studies

- They differ from RCTs in that randomization should control of confounders
- Cohort studies may still have confounders in ‘exposure’ vs. ‘unexposed’.
- Nevertheless, they help determine the ‘direction’ of relationship
- However, if the rate of the condition is low, then it may take a very large population many years to have significant power

Prospective Cohort

- Prospective trials allow uniform definitions and testing where as restrospective studies may be biased by indication
- But, subjects may change behaviors because they are prospectively followed
- Attrition of subjects
- Not as useful for rare diseases
- VERY Expensive

Retrospective Cohort

- People don't change behaviors via observation
- Lack of uniformity in testing?
- Can only test variables recorded and maybe by different definitions
- Can examine risky behaviors, unethical behaviors
- Less expensive and time consuming than prospective

Case-Control Studies

- If a condition is so rare or uncommon that it would take many years of follow-up in a cohort study (or randomized trial), a case-control study is an appropriate design
- Controls
  - Ideally disease free; if rare, then you can estimate the number in your controls that have the condition.
  - May wish to match on variables that may affect the outcomes such as age, race or sex or geographic region
  - Preferably identification of controls is random selection
  - Spouses, friends, relatives may have biases in matching
  - Hospital based controls similarly accessed the hospital system for some reason
  - Random digit dialing should include cell-phone only users to avoid biases
    - Cost runs from $20 to $75 per control identified depending on the number of criteria

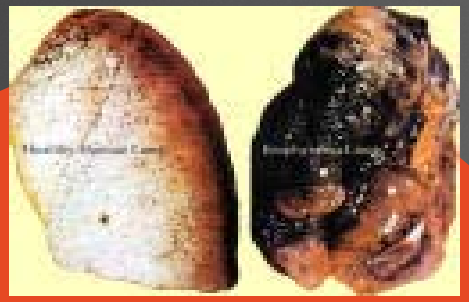
Association

- Two factors occur together more often than expected to by chance alone
- African-Americans have a higher rate of stroke than whites
- But, skin pigmentation does not appear to be ‘mechanistically’ or ‘causally’ associated with stroke
- The association is likely a ‘confounder’ for some other factor (like Hypertension).

Association

- However, AA's do have
  - Higher prevalence of salt-sensitive hypertension
  - And untreated hypertension
- These factors are not only associated with stroke, but are mechanistically related.
- Still, causality is not demonstrated by these observations.

Association



Lung Cancer

Caffeine

Causality

- Cause and Effect
- This suggests a ‘direction’ of relationship. Theoretically, association may go in either direction or have no directionality to it at all (just coincidence)
- In general, observational studies provide **supporting** evidence of causality
- However, one must be careful to avoid confounders!

Confounding

- Two factors that are associated with one another (occur together more often than by chance alone)
- Both factors will therefore be ‘associated’ with an outcome that one of them *causes*

Causality

Mechanism

Smoking

Lung Cancer

Confounding

Protective Effect

- This suggests that something decreases the risk of an outcome
- Treatment of hypertension is associated with a decreased risk of heart disease.
- The terms ‘causal’ and ‘protective’ are best demonstrated through RCTs or through prospective cohort studies

Studies that may demonstrate ‘causality’

- Randomized controlled trials
  - Theoretically, any confounders should have been randomized between groups, even the ones you don’t know about
- Prospective cohort studies
  - Theoretically, if some are ‘exposed’ at the onset and some are not, then if the outcome occurs more often in the exposed, this demonstrates a direction of effect; residual confounding is still possible but less likely
- Retrospective cohort studies
  - Theoretically, can also demonstrate causality but there is a risk of bias in identification of the outcomes.
- Case-Control
  - Certain aspects can demonstrate ‘causality’ although risk of confounding is highest. Usually best to assume association

Internal vs. External Validity

- External validity refers to whether or not the study is representative of all cases
  - Academic only/ single institution studies maybe biased towards more severe or unique populations
  - Multi-center or population-based studies can compare across institutions or include academic and community based institutions
- Internal validity refers to whether or not what they measured actually measures what they say they are measuring
  - How valid is asking someone if they have ever had a history of hypertension? (Roughly 70%)

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Why isn't everything an Observational Study?

- Residual Confounding – After controlling for other variables that you know of, there maybe relationships that you are not aware of.
  - The boogie man criticism – How do you know that the relationship you are seeing isn't caused by the boogie man?
- Confounding by indication – People who are exposed to a particular factor or drug may be exposed to it because they have the condition
  - Is hyperosmolar therapy associated with brain herniation and death? Or do really sick people who are likely to herniate more often treated with hyperosmolar therapy?
- Reverse Causality – Does drinking diet coke cause obesity and cardiac disease? Or, does being obese mean someone is more likely to drink diet drinks?

Beauty of Randomization

- Theoretically, randomization should randomize the boogie man (any residual confounders you aren't aware of) between groups and both confounding by indication and reverse causality are addressed by randomizing participants

Existing Databases

- The simplest way is to ask those that have already developed a database for access. Nearly every disease has someone that is studying the epidemiology of that disease
- Search pubmed for the disease and some useful key terms to trim down the numbers
  - "Population-Based"
  - "Prospective Cohort"
  - "Retrospective Cohort"

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Text availability
Abstract
Free full text
Full text

Publication dates
5 years
10 years
Custom range...

Species
Humans
Other Animals

Clear all

Show additional filters

Format: Summary **Sort by**: Most Recent **Per page**: 20 **Send to**

Best matches for amyotrophic lateral sclerosis population-based:

Variation in worldwide incidence of **amyotrophic lateral sclerosis**: a meta-analysis.
Marin B et al. Int J Epidemiol. (2017)

Analysis of **amyotrophic lateral sclerosis** as a multistep process: a **population-based** modelling study.
Al-Chalabi A et al. Lancet Neurol. (2014)

The changing picture of **amyotrophic lateral sclerosis**: lessons from European registers.
Hardiman O et al. J Neurol Neurosurg Psychiatry. (2017)

Switch to our new best match sort order

Search results

Items: 1 to 20 of 291

<< First < Prev Page 1 of 15 Next > Last >>

1. Risk of **amyotrophic lateral sclerosis** and other motor neuron disease among men with benign prostatic hyperplasia: a **population-based** cohort study.
Sørensen TT, Horváth-Puhó E, Nørgaard M, Ehrenstein V, Henderson VW.

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Reaching Out

- Each paper will have information about the study design and likely an attribution to the study for clinicaltrials.gov.
- In addition, a corresponding author or principal investigator for the study in question along with an email contact.
- The vast majority are likely to respond positively.
- Public records searches can also provide case report forms (not filled out) to evaluate if you can use for your study/analysis

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Proposed study

- Oxygen for acute ischemic stroke
- Reached out to Greater Cincinnati/Northern Kentucky Stroke Team: Population-based epidemiology of ischemic stroke study
  - What proportion of patients are already treated with oxygen prior to arrival to the emergency room?
  - What are the risk factors for patients to receive oxygen prior to arrival compared to those that aren't treated?
- Abstract presented at the International Stroke Conference
  - 68% of ischemic stroke patients receive supplemental oxygen
  - Lower GCS and higher NIHSS
  - Manuscript submitted

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Proposed Study

- Low cholesterol is associated with increased risk of brain hemorrhage (ICH)
- Lobar hemorrhage is associated with increased risk of recurrent hemorrhage
- Should patients with lobar hemorrhage on a statin at admission be continued on a statin?
  - Evaluated GERFHS/ERICH studies for the rate of ICH patients coming in with statins, rate of them being discharged on statins and rates of recurrent ICH as preliminary data
- Resulted in publication and major R01 funding!

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Proposed Study

- Treatment of hypertension after ICH with a polydrug
- Report that only 30% of all patients with ICH and hypertension are actually taking their anti-hypertensive medication at 6 month follow-up from the early 2000s; theoretically polydrug may improve compliance and treatment
- An evaluation of a US study found that 73% of all patients with hypertension were taking their anti-hypertensive medication at 6 month follow-up, access to healthcare was the major risk factor for non-compliance which would not be addressed by the polydrug
- This preliminary data substantially changed the grant

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Recruitment Potential/Feasibility

- Basic inclusion/exclusion criteria:
  - Depending on your study, you can determine how may patients you are excluding based on your criteria
  - In general, sites can provide you with ICD9/10 code data on the total number of patients seen at your institution and with specific criteria such as age range
  - Severity scores – Many available datasets can tell you what proportion of patients can be expected to have your severity criteria

Flaherty et al

- Evaluated the population area that you would need to identify sufficient cases of warfarin related ICH to identify effect sizes of 2.5% to 20% if the standard therapy had a rate of 55% poor outcomes
  - For 20% effect size, would need a base population of 52 million people; roughly 1/6th of the United States
  - For 2.5% effect size, would need a population based of 3.4 BILLION people or roughly half the planet!

Table 2. Eligibility Rates and Necessary Population Base for WICH Treatment Trials

	Criteria Set 1			Criteria Set 2			Criteria Set 3		
	Standard Therapy Rate of Poor Outcome=55%			Standard Therapy Rate of Poor Outcome=65%			Standard Therapy Rate of Poor Outcome=75%		
Effect Size* (%)	Sample Size	Eligible†	Area‡	Sample Size	Eligible†	Area‡	Sample Size	Eligible†	Area‡
2.5	12 500	2	3.4×10^{9}	11 620	6	1.0×10^{9}	9720	11	4.8×10^{8}
5	3130	2	8.4×10^{8}	2944	6	2.6×10^{8}	2500	11	1.2×10^{8}
10	784	2	2.1×10^{8}	752	6	6.7×10^{7}	656	11	3.2×10^{7}
15	346	2	9.3×10^{7}	340	6	3.0×10^{7}	302	11	1.5×10^{7}
20	192	2	5.2×10^{7}	192	6	1.7×10^{7}	176	11	8.6×10^{6}

*Absolute reduction in poor outcome (mRS score 4–6) at 90 days.

†N of eligible patients in the GCNK region (of ≈1.3 million) per year.

‡Given calculated sample size and eligibility rates, population base needed to complete trial enrollment in 5 years. Assumes enrollment of 50% of eligible subjects.

Writing an observational study

- If the study is criticized as unrealistic, not-feasible, not enough preliminary data
  - Sometimes the only thing that can answer such a critique is to perform a mini-version of the study or an earlier phase (Phase 0 or Phase 1)
- But sometimes can be addressed with developing some preliminary data;
  - Biases are the reason you need a more definitive study; don't avoid them, embrace them as part of your rationale

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Writing a simple retrospective chart review

- Review cases within your electronic medical records
- Retrospective case or case versus control study
- Develop a case report form and a data dictionary
  - The data dictionary defines each term on your case report form and the range and uniform reporting
- Develop an IRB Protocol with HIPAA waiver to perform the retrospective chart review
- Redcap or other secure database that can be pulled for analyses

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Electronic Medical Records Search

- Although largely single institution, often times it's better than nothing
- Most electronic medical records searches will allow you to identify how many but won't let you look into the actual records.
- Slicer/Dicer is in Epic and easily allows you to search on diagnoses, meds, age ranges
- TriNetX and other platforms allow you to search on many keyterms
- EMERSE allows you to look at the vast majority of reports such as H&P, discharge, progress reports and radiology reports

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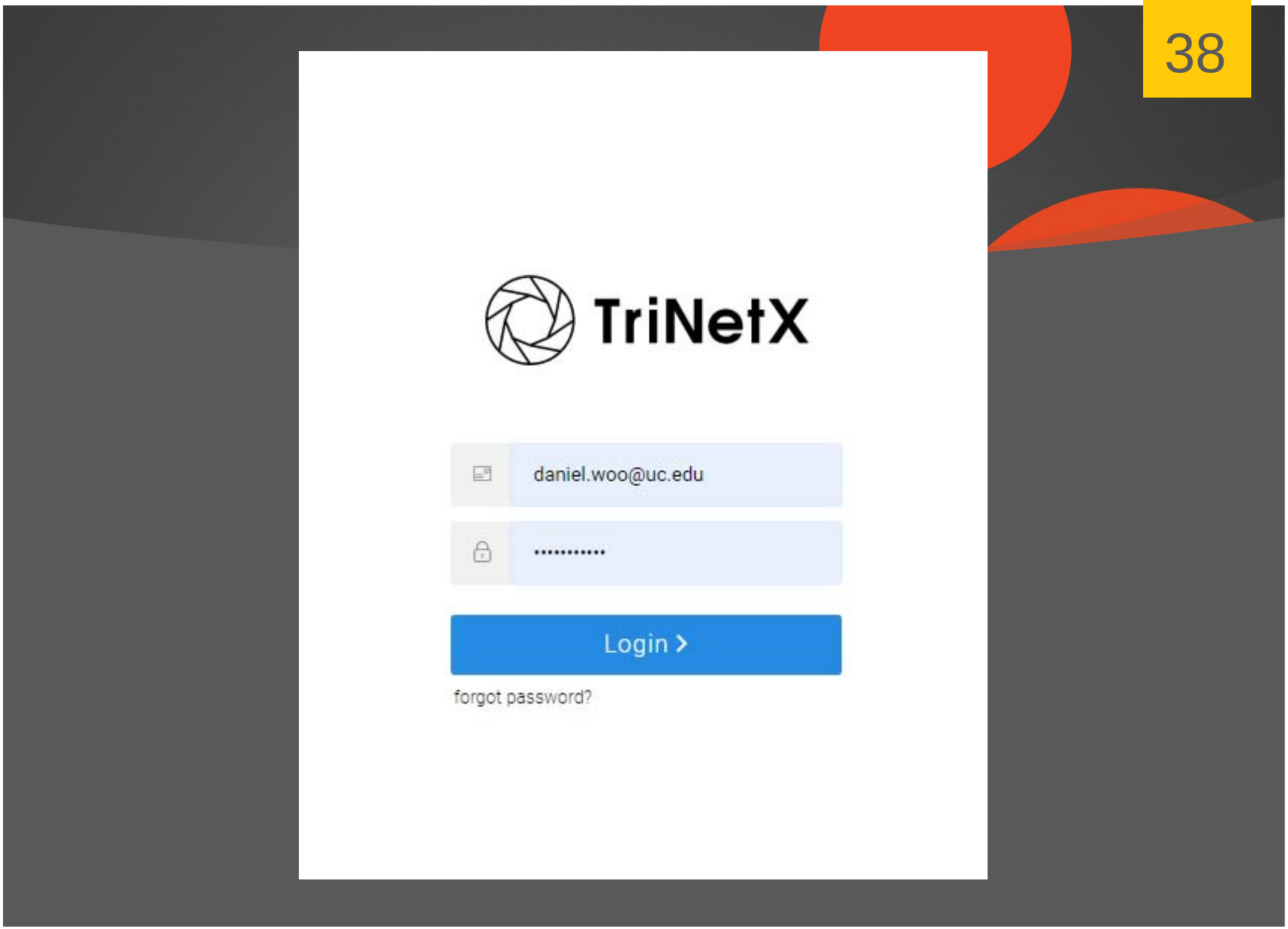

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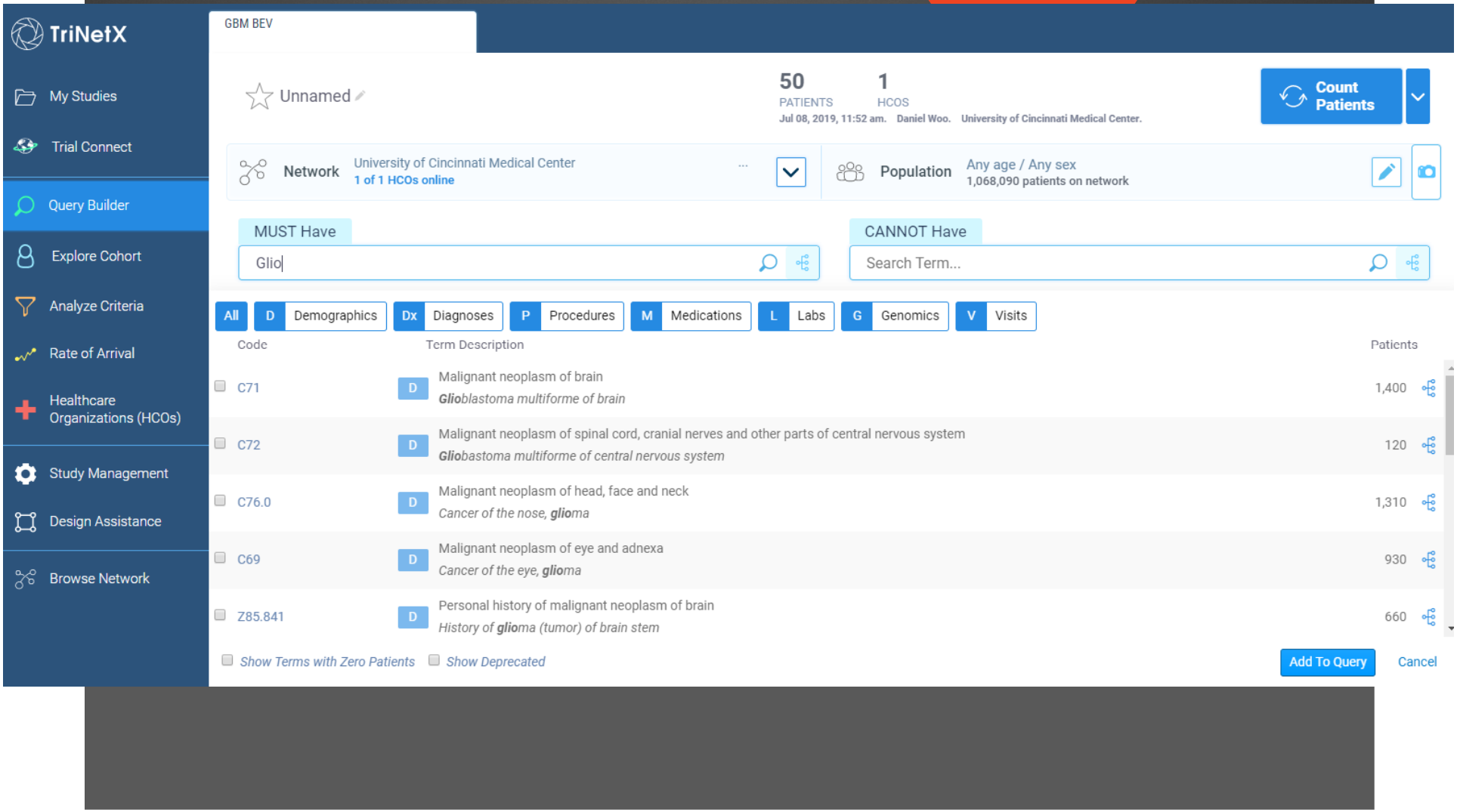

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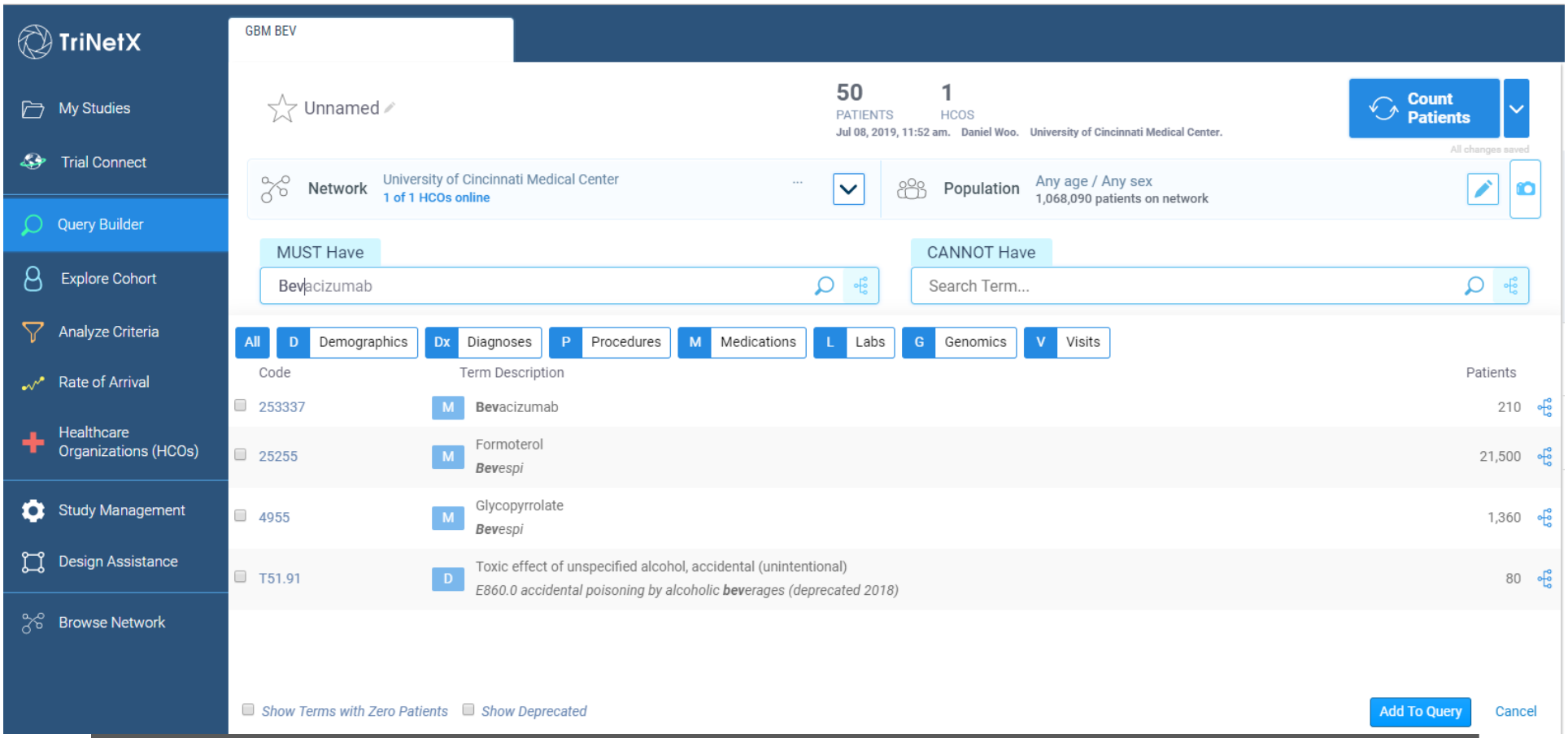
TriNetX
My Studies
Trial Connect
Query Builder
Explore Cohort
Analyze Criteria
Rate of Arrival
Healthcare Organizations (HCOs)
Study Management
Design Assistance
Browse Network
GBM BEV
Unnamed
50
PATIENTS
1
HCOS
Jul 08, 2019, 11:52 am. Daniel Woo. University of Cincinnati Medical Center.
Count Patients
All changes saved
Network
University of Cincinnati Medical Center
1 of 1 HCOs online
Population
Any age / Any sex
1,068,090 patients on network
MUST Have
Bevacizumab
CANNOT Have
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D Demographics
Dx Diagnoses
P Procedures
M Medications
L Labs
G Genomics
V Visits
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Term Description
Patients
253337
M
Bevacizumab
210
25255
M
Formoterol
Bevespi
21,500
4955
M
Glycopyrrolate
Bevespi
1,360
T51.91
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Toxic effect of unspecified alcohol, accidental (unintentional)
E860.0 accidental poisoning by alcoholic beverages (deprecated 2018)
80
Show Terms with Zero Patients
Show Deprecated
Add To Query
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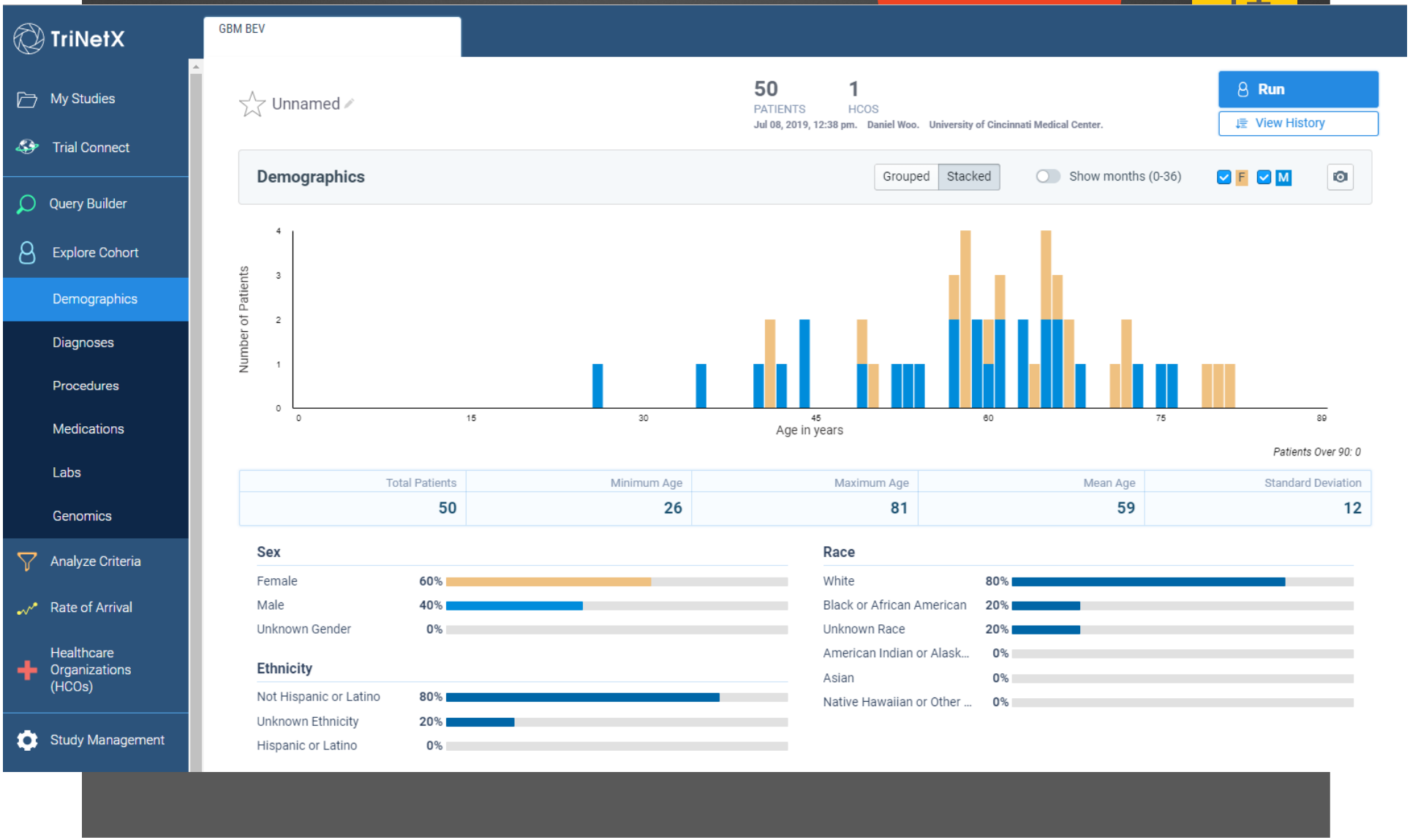

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GBM and BEV

- Found 50 patients of which 10 were over 65 years of age (the target for the study).
  - Can perform a retrospective chart review of these patients for adverse event rates, Karnofsky scores?
  - Can also go back to the larger group of GBM patients and match by age and Karnofsky score to those that received Bev
- There are many flaws and biases to this but it may provide some data on tolerability

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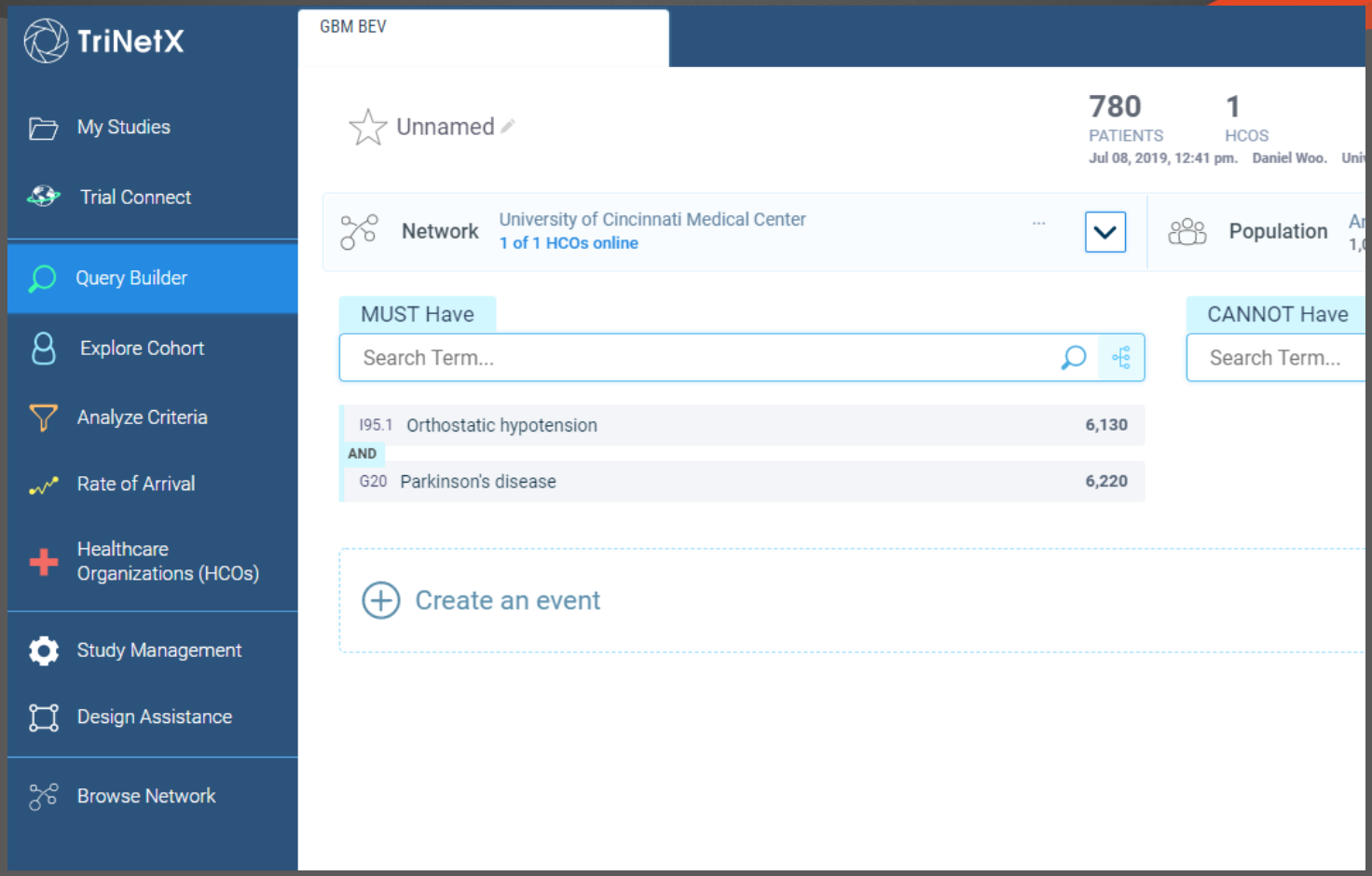
Orthostatic Hypotension and Droxidopa



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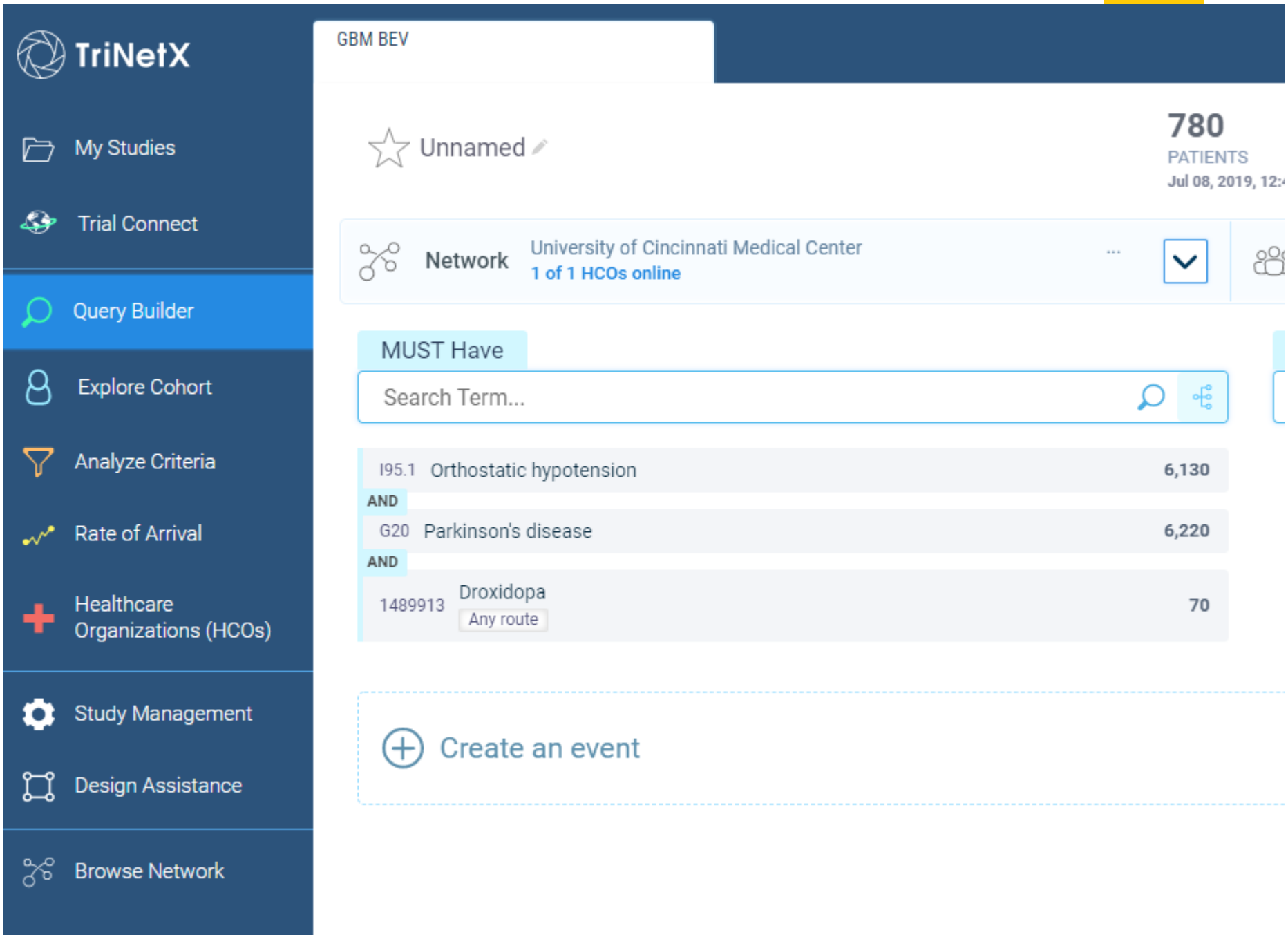
TriNetX
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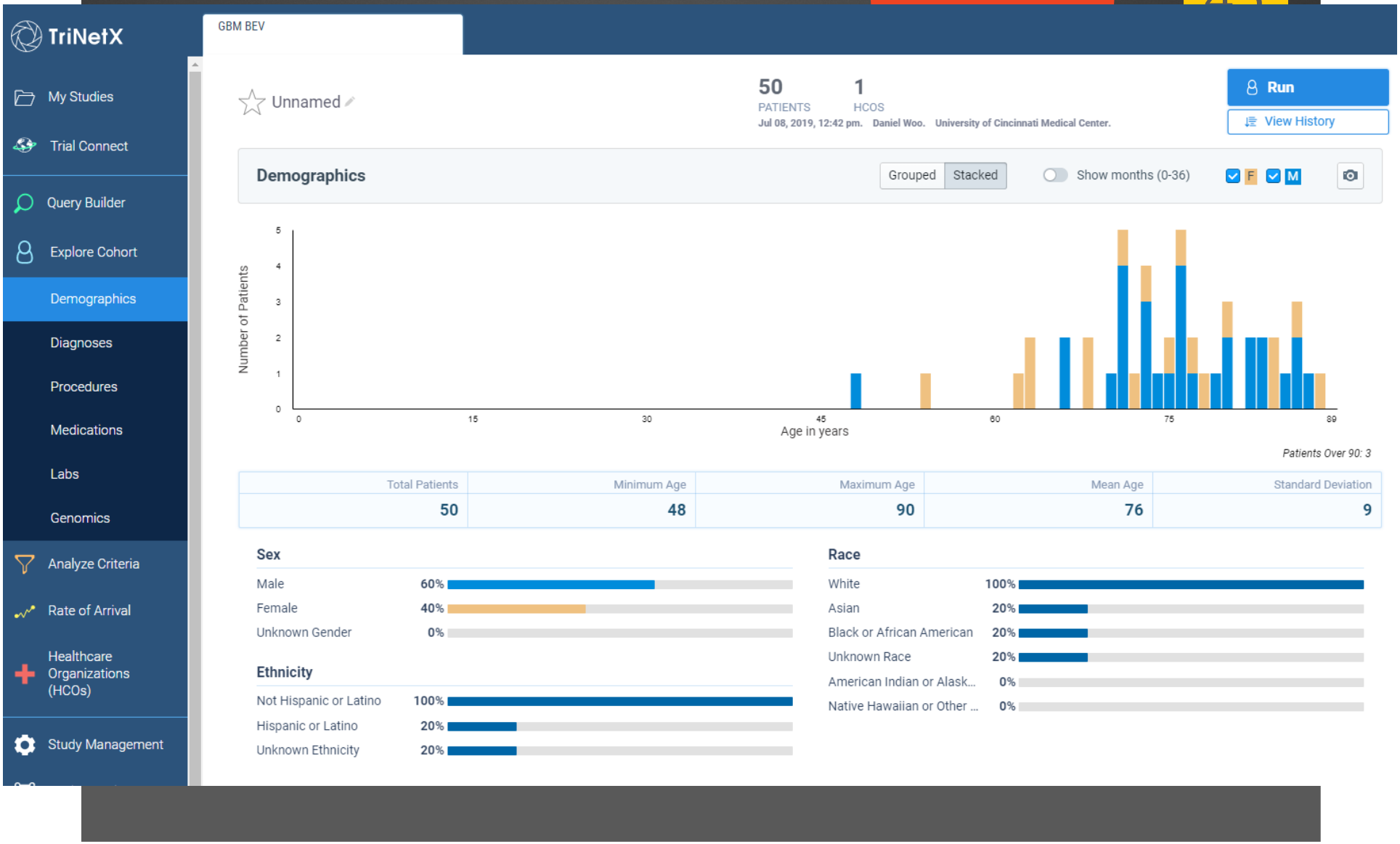
Healthcare Organizations (HCOs)
Study Management
Design Assistance
Browse Network
Unnamed
780
PATIENTS
Network
University of Cincinnati Medical Center
1 of 1 HCOs online
MUST Have
Search Term...
I95.1 Orthostatic hypotension 6,130
AND
G20 Parkinson's disease 6,220
AND
1489913 Droxidopa
Any route
70
Create an event



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- From this dataset, you can add in criteria like history of dementia and see how many people you may lose
- You can add in ‘dementia’ or ‘statins’ or other terms to see how many patients are lost with each item that you add out of the entire group
- We already know 70 out of 780 were already treated with droxidopa or 8.9% lost
- When I add any history of any dementia, lose 110 (14.1%)
- If I add in cannot be on midodrine, I lose 350 patients! (44.8%)

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Chart Review

- Once you have the dataset, in general, most institutions have a way of sending you the medical record numbers if you have an IRB approved protocol that will allow you then to review the charts
- 50-100 charts is definitely doable in a month or so.

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Summarize

- Observation is the first step in the scientific method
- Many questions with rare outcomes require observational studies to perform
- But observational studies may have critical biases that require testing
- Can obtain observational data from other large studies already in existence (and publish!)
- Can perform simple chart reviews utilizing the powerful electronic medical tools already available to you

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Questions?

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