DOC Data – Advanced Training

September 7, 2017
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DOC Data – Advanced Training Objectives

After this training, participants will be able to:

1. Understand DRE methodology and how to jointly conduct projects
2. Navigate DOC Data platform and execute analytical methods
3. Use descriptive statistics and visualizations to prepare data for analysis
4. Perform Cohort Analysis, Direct Meta-Analysis, and Bayesian Network Meta-Analysis

DRE - Sanofi Engagement

Doctor Evidence is in the first year of **a multi-year engagement** with Sanofi -- executive sponsors are Ameet Nathwani and Bernard Hamelin

Direct access to DRE platforms with training and Single Sign On

Project services for identified needs (PICO process)

Deliverables to Serve Functions & GBUs

Deliverables

- Systematic Literature Reviews
- Network Meta Analyses
- Landscape Assessments
- Safety Analyses
- Competitor Label Review
- Regulatory Responses
- Responsive Communications (HCP and Payer)

Functions

- Medical
- Health Economics
- Outcomes Research
- Patient Centricity
- Scientific Communications and Publications
- Clinical Development
- Biostatistics
- Safety and Epidemiology

GBUs

- DCV
- Genzyme
- GEM
- CHC

DOCTOR EVIDENCE
Turning data into knowledge

DRE - Sanofi MSA

There is no additional cost to Sanofi users for any services. All fees are covered under the existing Master Services Agreement.

Our mission is to find, synthesize, and analyze medical data from all sources into fit-to-purpose actionable knowledge.

DRE is a medical evidence company.

What does DRE do?

- Identify relevant published literature to answer scientific questions and extract data from these sources using proprietary software technologies
  - Create libraries, curated and searchable
  - Create relational databases suitable for analyses
- Consult with our clients to provide meaningful insights that inform decisions and guide tactics
  - Structured consulting process
  - Frequent and regular touchpoints with our clients
  - Deliverables include written reports, slide decks and publications

Joint DRE-Sanofi Workflow Process

	Business Question	PICO Protocol	Literature Search and Screen	Review of Library Results	Data Configuration	Analysis and Interpretation
DRE Process		Joint collaboration to draft PICO Protocol	DRE conducts literature search and screen into DOC Library	Joint review of search results	DRE conducts data configuration into DOC Data	DRE and/or Sanofi produce analytics
Sanofi Process	Sanofi submits business question					

Workflow Process from Beginning to End

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Doctor Evidence Process

Question → Scoping → PICO → Search and Screen → DOC Library → Data Configuration → DOC Data → Analysis and Delivery → ✓ Deliverables

Business Need

- Identification of project
- Alignment with strategic needs

Guiding Documentation

- Selection of inclusion/exclusion parameters
- Clinical, Methodological input

Searchable Library

- Compilation of relevant documents in central location
- Index of all medical terms in documents

Actionable Database

- Extraction of key variables with statistics, definitions, and ontological context
- Meta-analysis or other appropriate methods used to generate results

Valuable Outputs

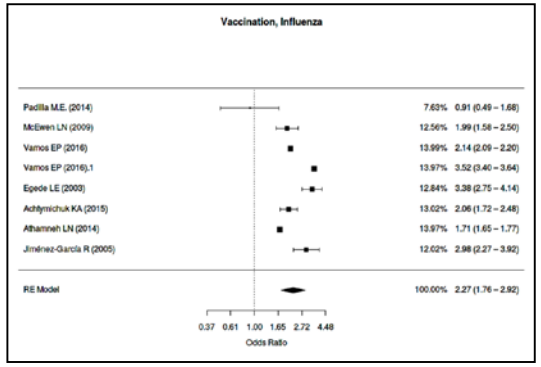
- Systematic Literature Reviews
- Network Meta-Analyses
- Disease Landscape Assessments
- Safety Assessments

Doctor Evidence – Evidence Synthesis Process

Data Source (e.g. PDF) → Data Extraction → Digitized Studies → Ontology Management → DOC Data → Analysis → Work Product → SLRs, Publications, Submissions, etc.

PDF article

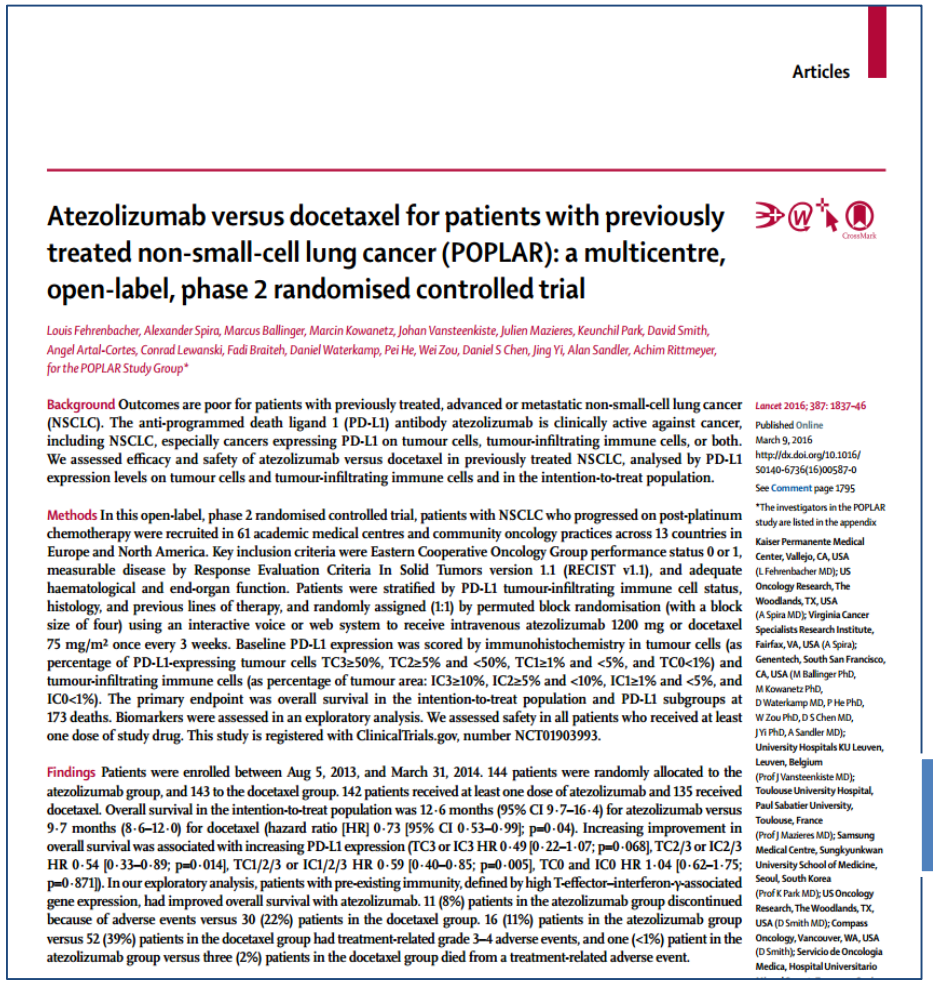
Digital Study



Meta-Analysis

Publication

Data Digitization into DOC Data



Articles

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

*Louis Fehrenbacher, Alexander Spira, Marcus Ballinger, Marcin Kowanetz, Johan Vansteenkiste, Julien Mazieres, Keunchil Park, David Smith, Angel Artal-Cortes, Conrad Lewanski, Fadi Braiteh, Daniel Waterkamp, Pei He, Wei Zou, Daniel S Chen, Jing Yi, Alan Sandler, Achim Rittmeyer, for the POPLAR Study Group**

Background Outcomes are poor for patients with previously treated, advanced or metastatic non-small-cell lung cancer (NSCLC). The anti-programmed death ligand 1 (PD-L1) antibody atezolizumab is clinically active against cancer, including NSCLC, especially cancers expressing PD-L1 on tumour cells, tumour-infiltrating immune cells, or both. We assessed efficacy and safety of atezolizumab versus docetaxel in previously treated NSCLC, analysed by PD-L1 expression levels on tumour cells and tumour-infiltrating immune cells and in the intention-to-treat population.

Methods In this open-label, phase 2 randomised controlled trial, patients with NSCLC who progressed on post-platinum chemotherapy were recruited in 61 academic medical centres and community oncology practices across 13 countries in Europe and North America. Key inclusion criteria were Eastern Cooperative Oncology Group performance status 0 or 1, measurable disease by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), and adequate haematological and end-organ function. Patients were stratified by PD-L1 tumour-infiltrating immune cell status, histology, and previous lines of therapy, and randomly assigned (1:1) by permuted block randomisation (with a block size of four) using an interactive voice or web system to receive intravenous atezolizumab 1200 mg or docetaxel 75 mg/m² once every 3 weeks. Baseline PD-L1 expression was scored by immunohistochemistry in tumour cells (as percentage of PD-L1-expressing tumour cells TC3≥50%, TC2≥5% and <50%, TC1≥1% and <5%, and TC0<1%) and tumour-infiltrating immune cells (as percentage of tumour area: IC3≥10%, IC2≥5% and <10%, IC1≥1% and <5%, and IC0<1%). The primary endpoint was overall survival in the intention-to-treat population and PD-L1 subgroups at 173 deaths. Biomarkers were assessed in an exploratory analysis. We assessed safety in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01903993.

Findings Patients were enrolled between Aug 5, 2013, and March 31, 2014. 144 patients were randomly allocated to the atezolizumab group, and 143 to the docetaxel group. 142 patients received at least one dose of atezolizumab and 135 received docetaxel. Overall survival in the intention-to-treat population was 12·6 months (95% CI 9·7–16·4) for atezolizumab versus 9·7 months (8·6–12·0) for docetaxel (hazard ratio [HR] 0·73 [95% CI 0·53–0·99]; p=0·04). Increasing improvement in overall survival was associated with increasing PD-L1 expression (TC3 or IC3 HR 0·49 [0·22–1·07; p=0·068], TC2/3 or IC2/3 HR 0·54 [0·33–0·89; p=0·014], TC1/2/3 or IC1/2/3 HR 0·59 [0·40–0·85; p=0·005], TC0 and IC0 HR 1·04 [0·62–1·75; p=0·871]). In our exploratory analysis, patients with pre-existing immunity, defined by high T-effector–interferon-γ-associated gene expression, had improved overall survival with atezolizumab. 11 (8%) patients in the atezolizumab group discontinued because of adverse events versus 30 (22%) patients in the docetaxel group. 16 (11%) patients in the atezolizumab group versus 52 (39%) patients in the docetaxel group had treatment-related grade 3–4 adverse events, and one (<1%) patient in the atezolizumab group versus three (2%) patients in the docetaxel group died from a treatment-related adverse event.

Lancet 2016; 387: 1837–46

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See Comment page 1795

*The investigators in the POPLAR study are listed in the appendix

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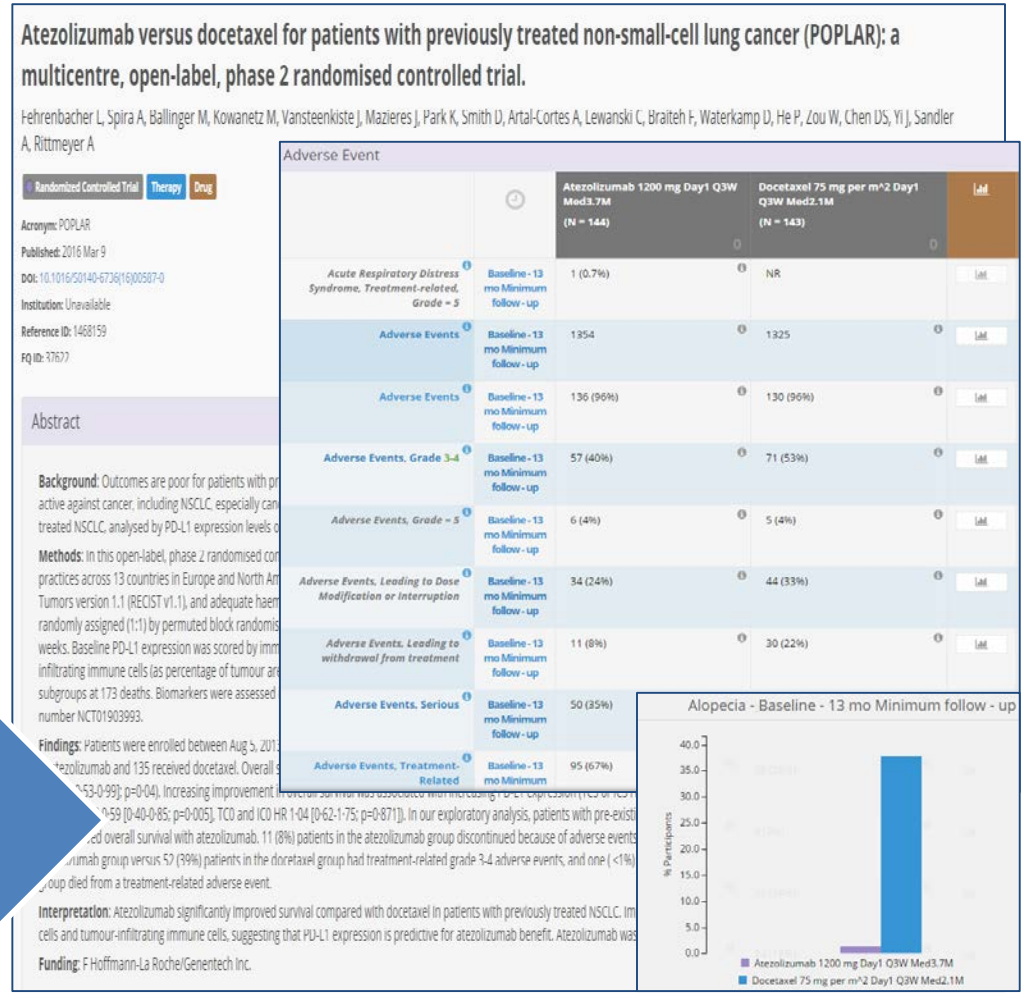

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial.

Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A, Rittmeyer A

Randomized Controlled Trial | Therapy | Drug

Acronym: POPLAR

Published: 2016 Mar 9

DOI: 10.1016/S0140-6736(16)00587-0

Institution: Unavailable

Reference ID: 1468159

FQ ID: 37677

Abstract

Adverse Event

		Atezolizumab 1200 mg Day1 Q3W Med3.7M (N = 144)	Docetaxel 75 mg per m^2 Day1 Q3W Med2.1M (N = 143)
Acute Respiratory Distress Syndrome, Treatment-related, Grade = 5	Baseline - 13 mo Minimum follow - up	1 (0.7%)	NR
Adverse Events	Baseline - 13 mo Minimum follow - up	1354	1325
Adverse Events	Baseline - 13 mo Minimum follow - up	136 (96%)	130 (96%)
Adverse Events, Grade 3-4	Baseline - 13 mo Minimum follow - up	57 (40%)	71 (53%)
Adverse Events, Grade = 5	Baseline - 13 mo Minimum follow - up	6 (4%)	5 (4%)
Adverse Events, Leading to Dose Modification or Interruption	Baseline - 13 mo Minimum follow - up	34 (24%)	44 (33%)
Adverse Events, Leading to withdrawal from treatment	Baseline - 13 mo Minimum follow - up	11 (8%)	30 (22%)
Adverse Events, Serious	Baseline - 13 mo Minimum follow - up	50 (35%)	
Adverse Events, Treatment-Related	Baseline - 13 mo Minimum	95 (67%)	

Alopecia - Baseline - 13 mo Minimum follow - up

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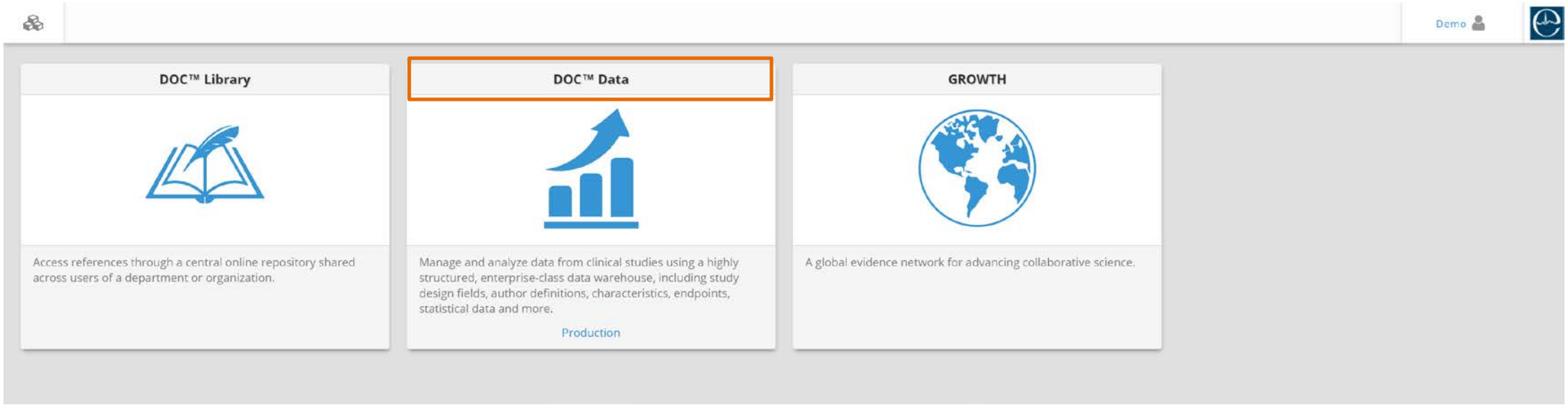
DOC Data Navigation: ALLOWS YOU TO LAUNCH ANY DOC APPLICATION



To log in to DOC Data, navigate to https://sanofi.doctorevidence.com. Please note that Chrome is the recommended browser.

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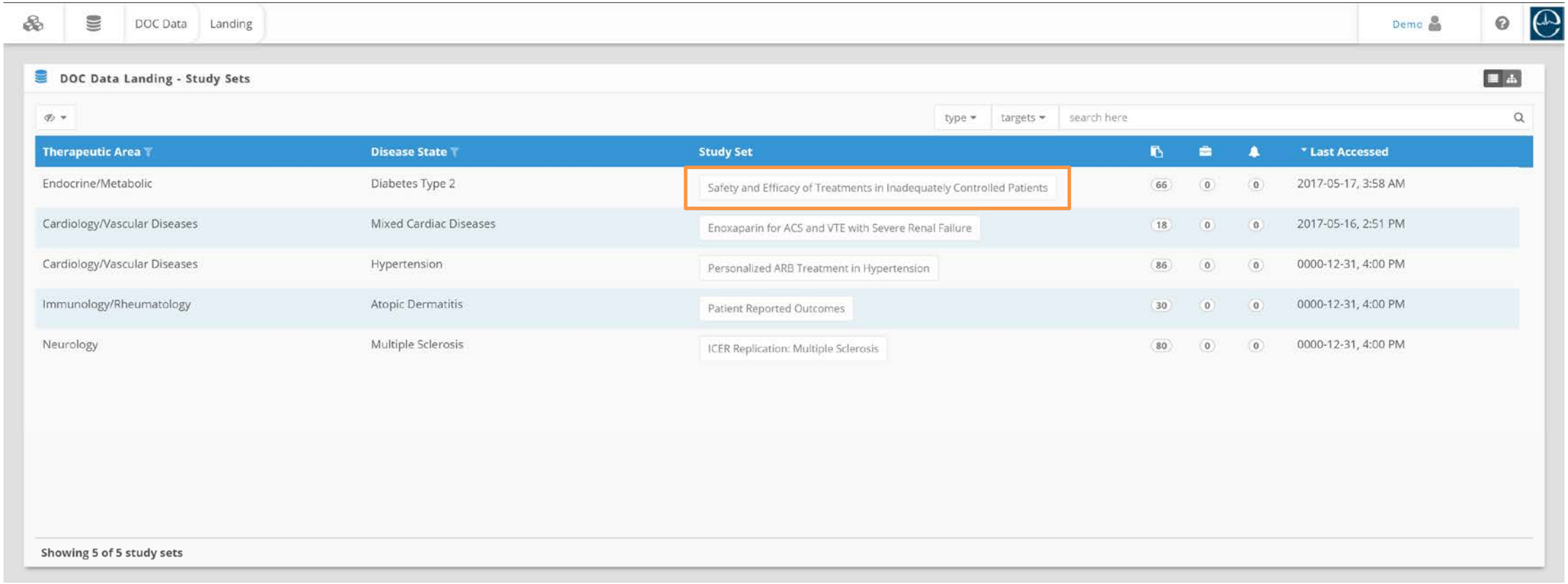
Turning data into knowledge

DOC Data Navigation

LANDING PAGE: ALLOWS YOU TO LAUNCH ANY STUDY SET

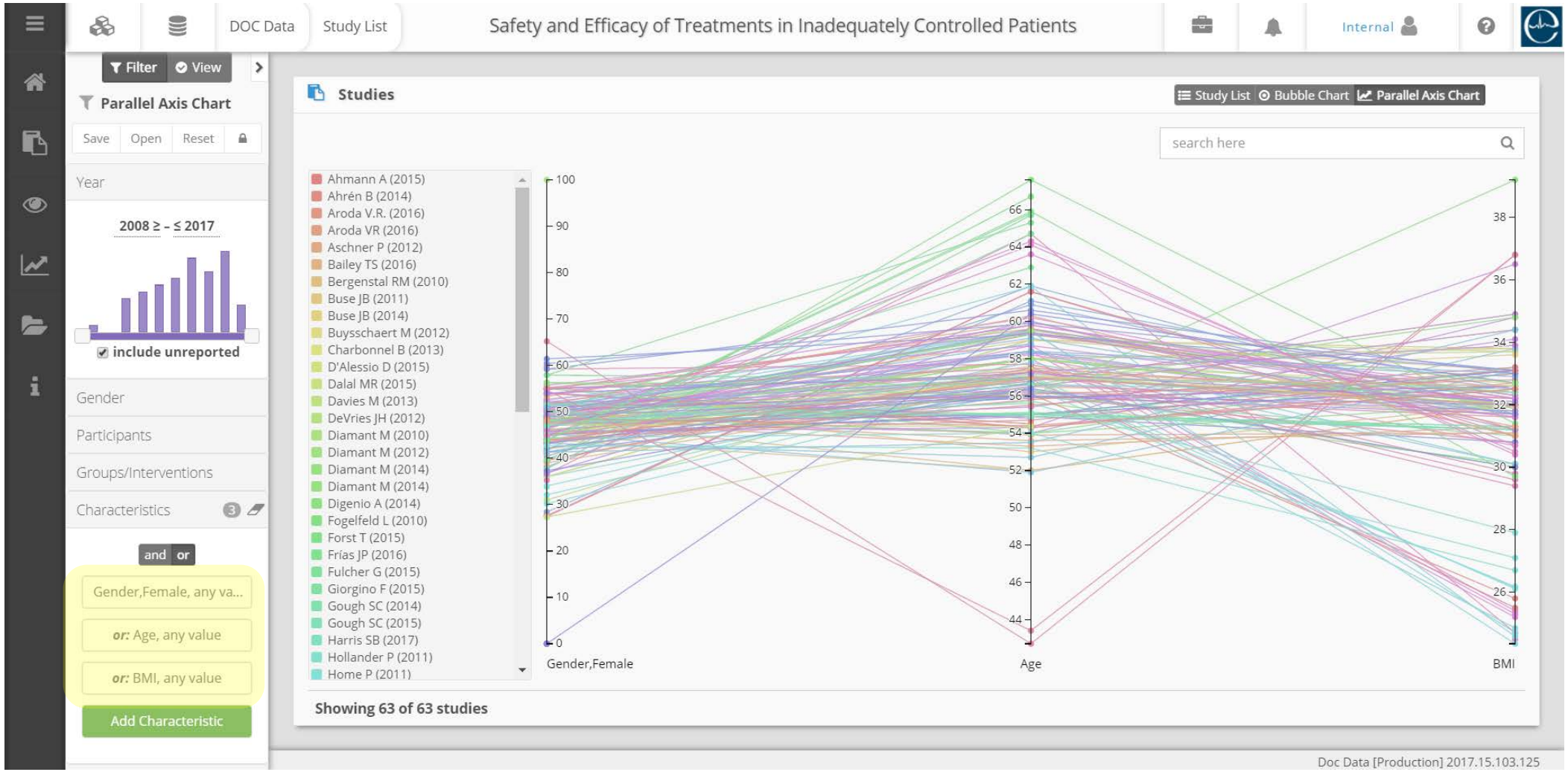


Sample Research Question ACTIVITY

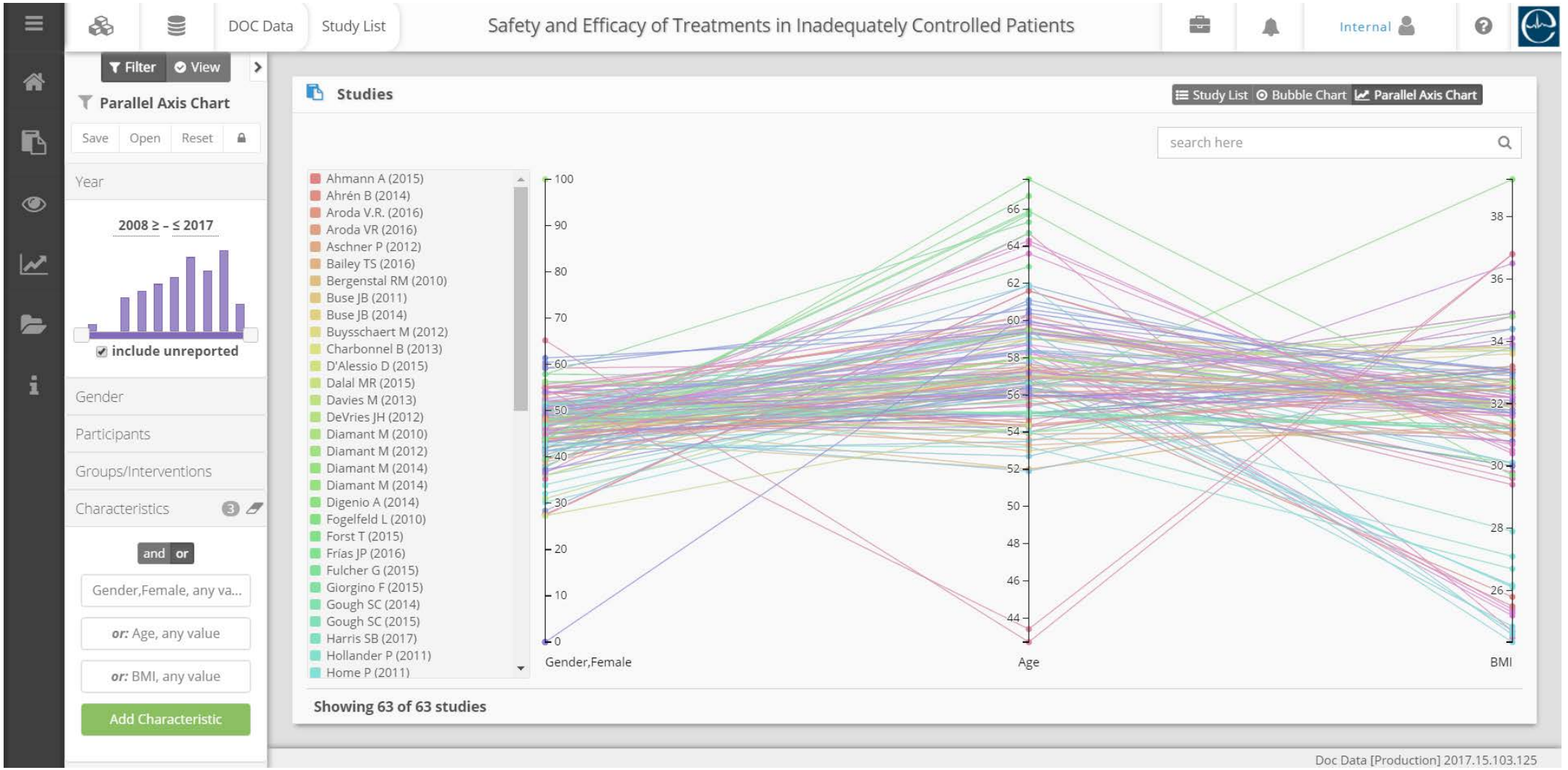
- Does Insulin Glargine effectively reduce HbA1c in patients with the following profile?
  - Age, >= 50
  - BMI, <= 35
  - Race, Caucasian, >= 70%
  - Gender Female, 40% to 60%

Descriptive Statistics & Visualizations: **Using the Parallel Axis Chart**

DOC Data – Parallel Axis Chart – Demo



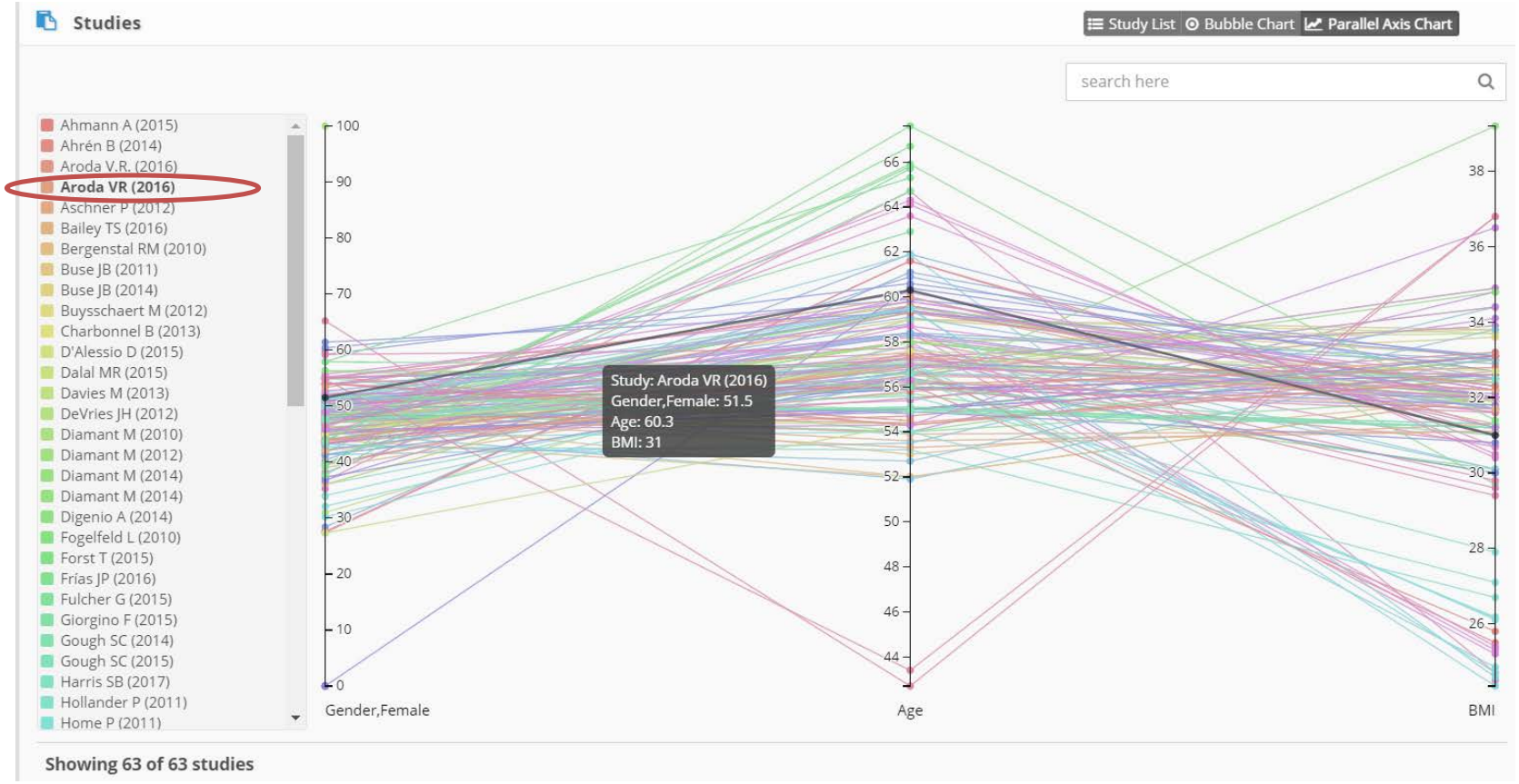
DOC Data – Parallel Axis Chart



This example added [Gender, Female], [Age], and [BMI]

DOC Data – Parallel Axis Chart

Each line represents a study. Hovering over it will bold it across the chart. You can access the study summary by selecting the study on the left bar



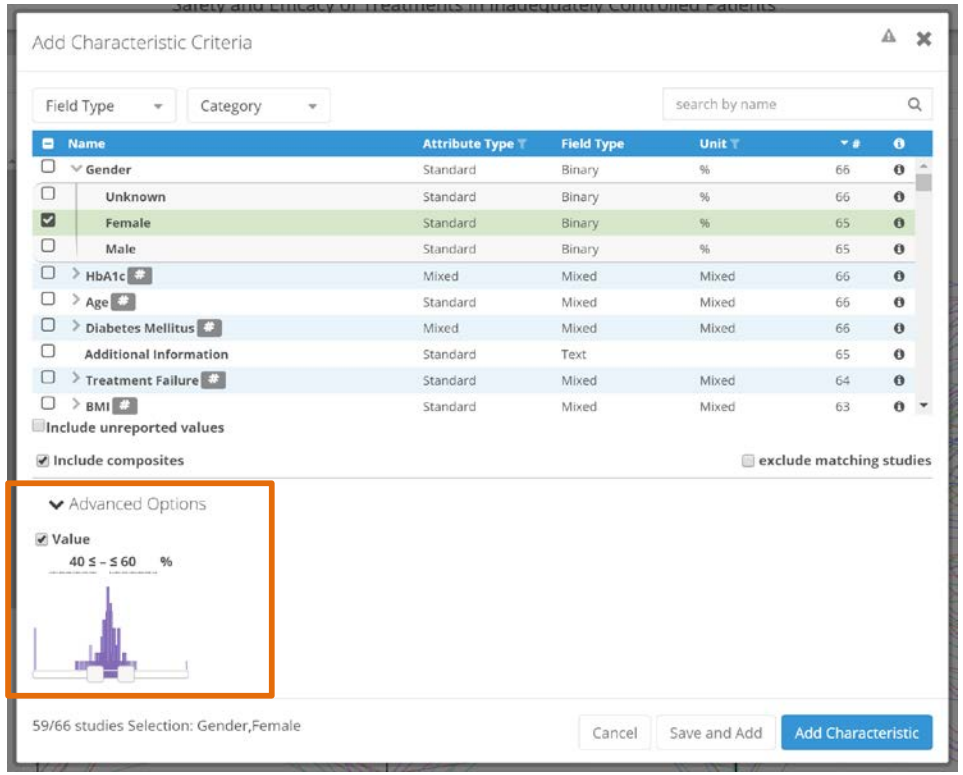
Parallel Axis ACTIVITY

1. Select ranges for the following:

- Age, >= 50
- BMI, <= 35
- Race, Caucasian, >= 70%
- Gender Female, 40% to 60%

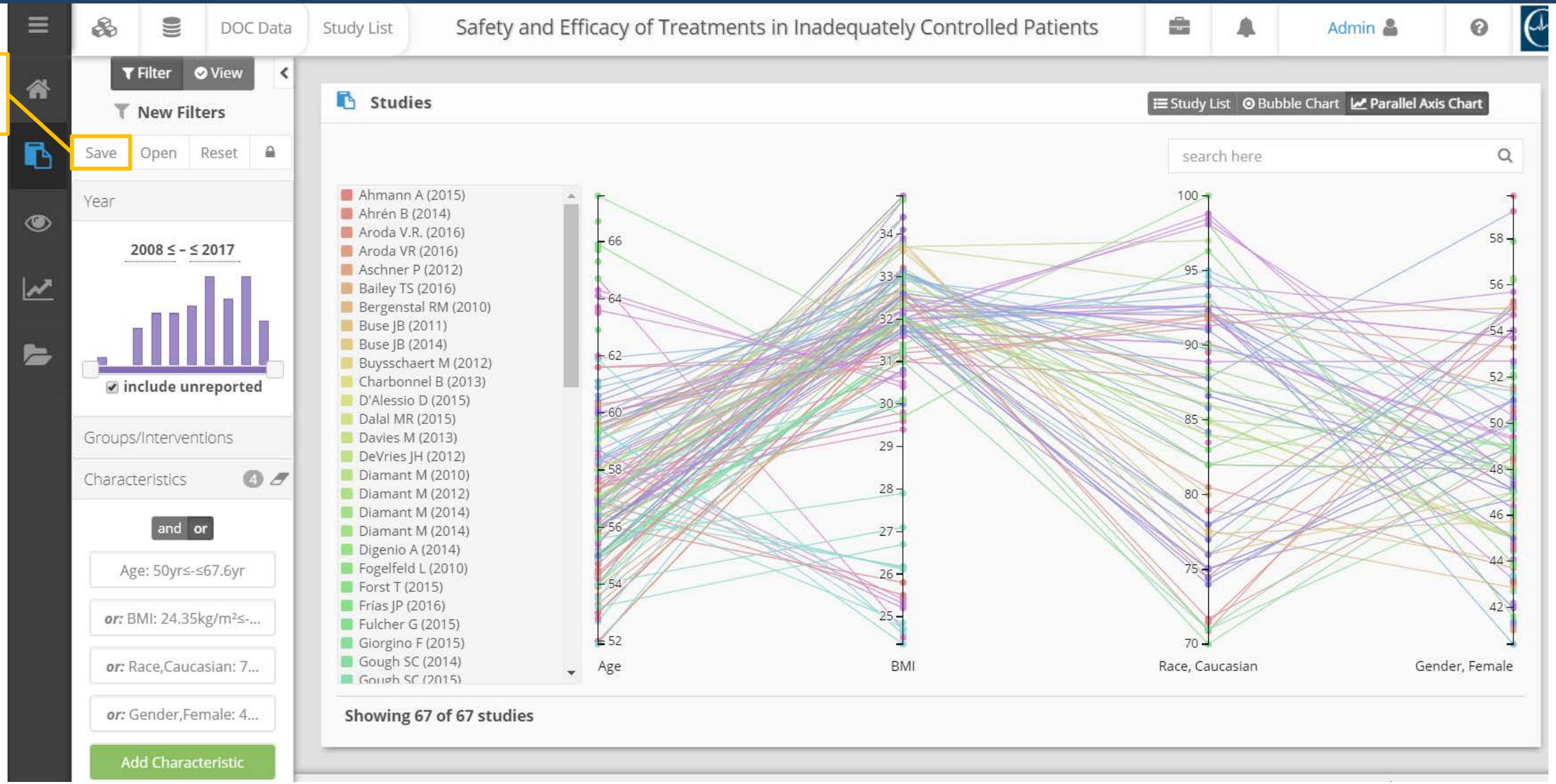
2. Save the filter set as a workflow so that it can be opened in other tools

Clue



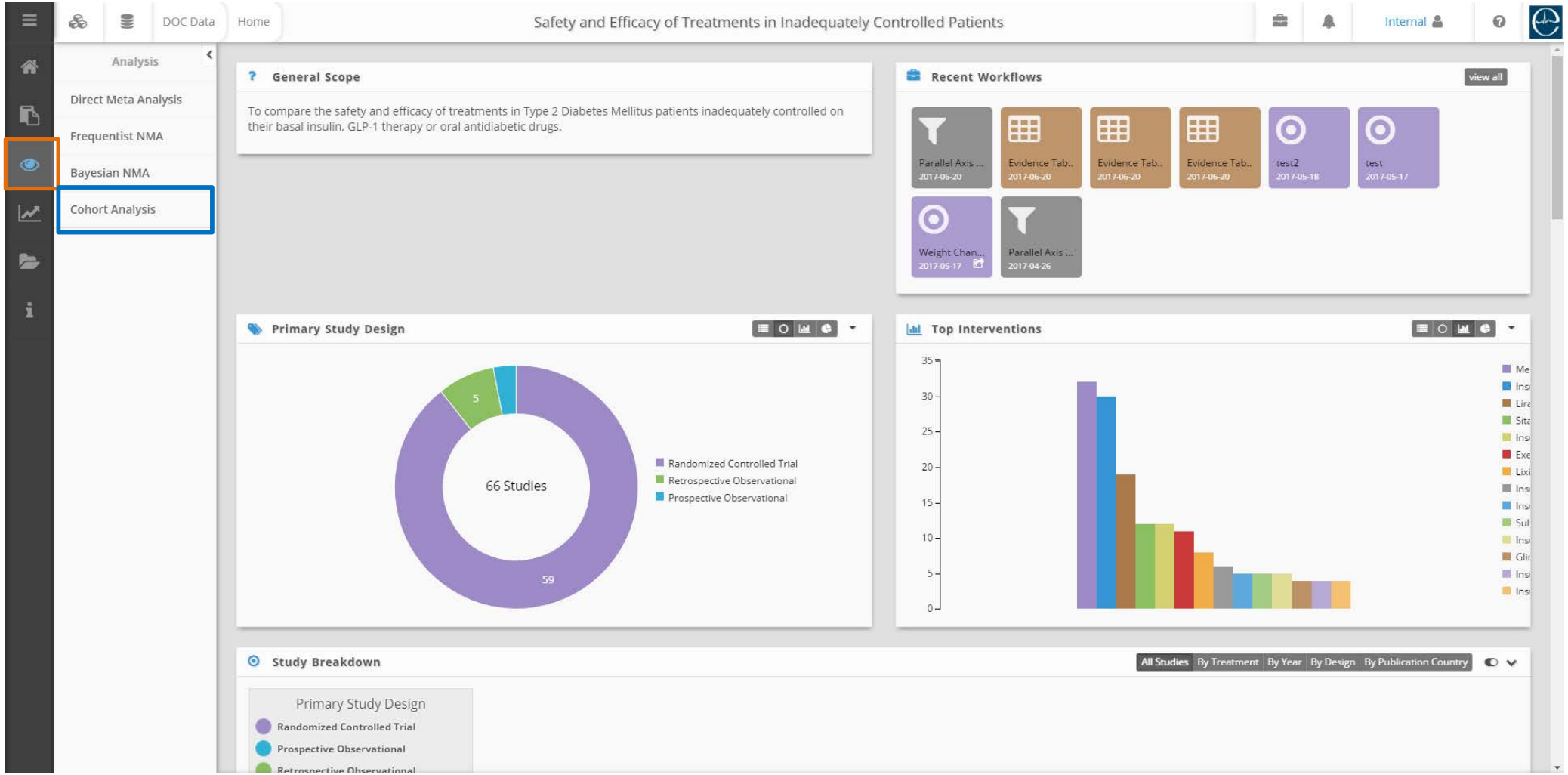
Parallel Axis ACTIVITY – output

Save this patient profile as a filter set



DOC Data:
Cohort Analysis

Cohort Analysis

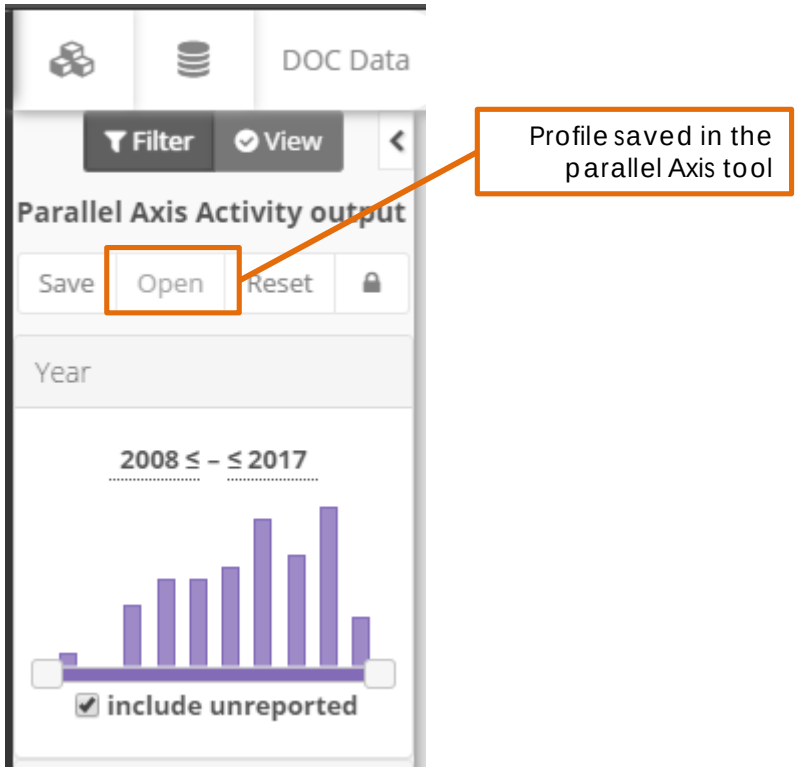


Cohort Analysis ACTIVITY

Does Insulin Glargine reduce HbA1c for patients with following profile?

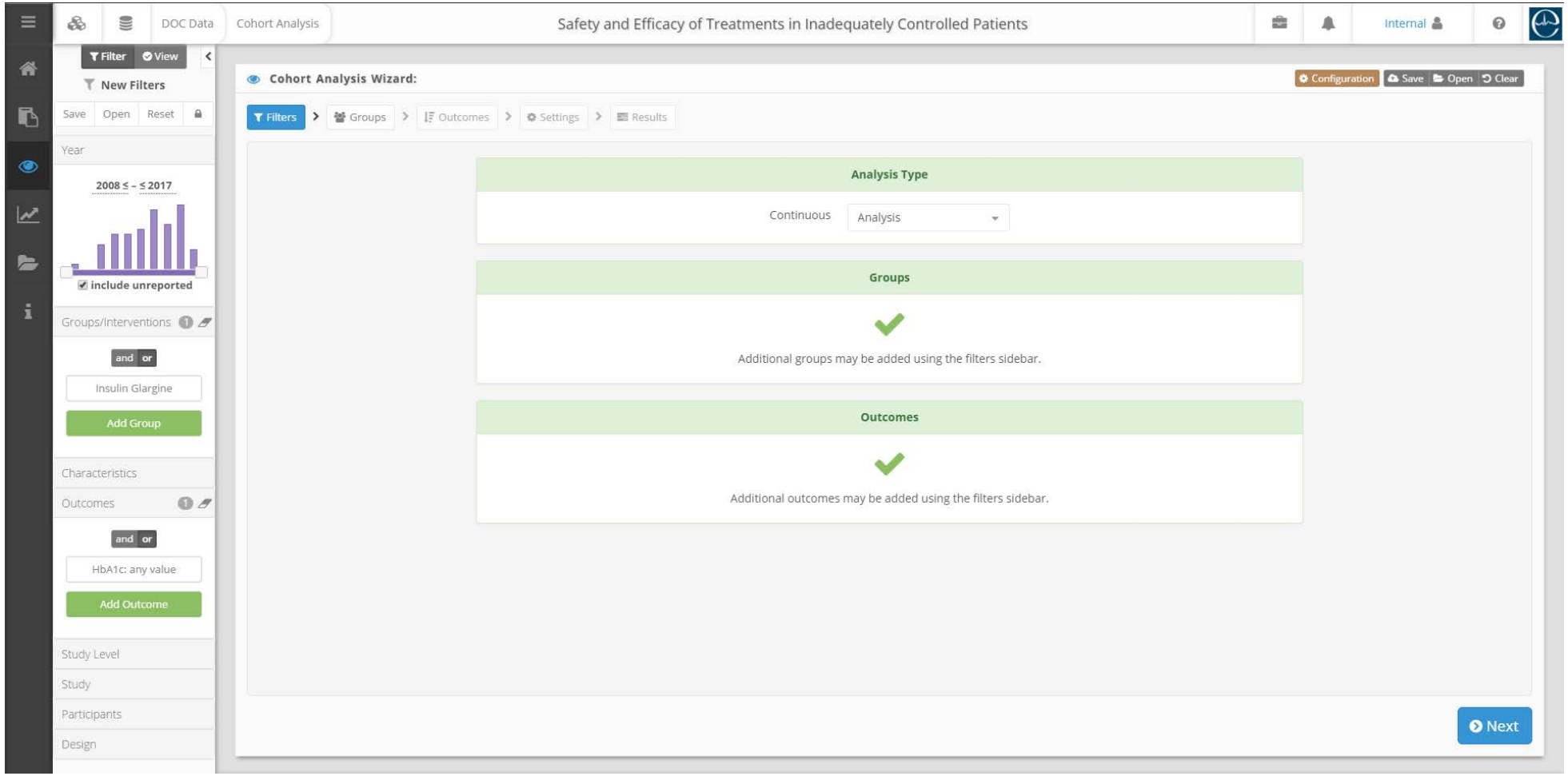
- **Age, >= 50**
- **BMI, <= 35**
- **Race, Caucasian, >= 70%**
- **Gender Female, 40% to 60%**

Clue



Cohort Analysis – Demo

Does Insulin Glargine Reduce HbA1c?



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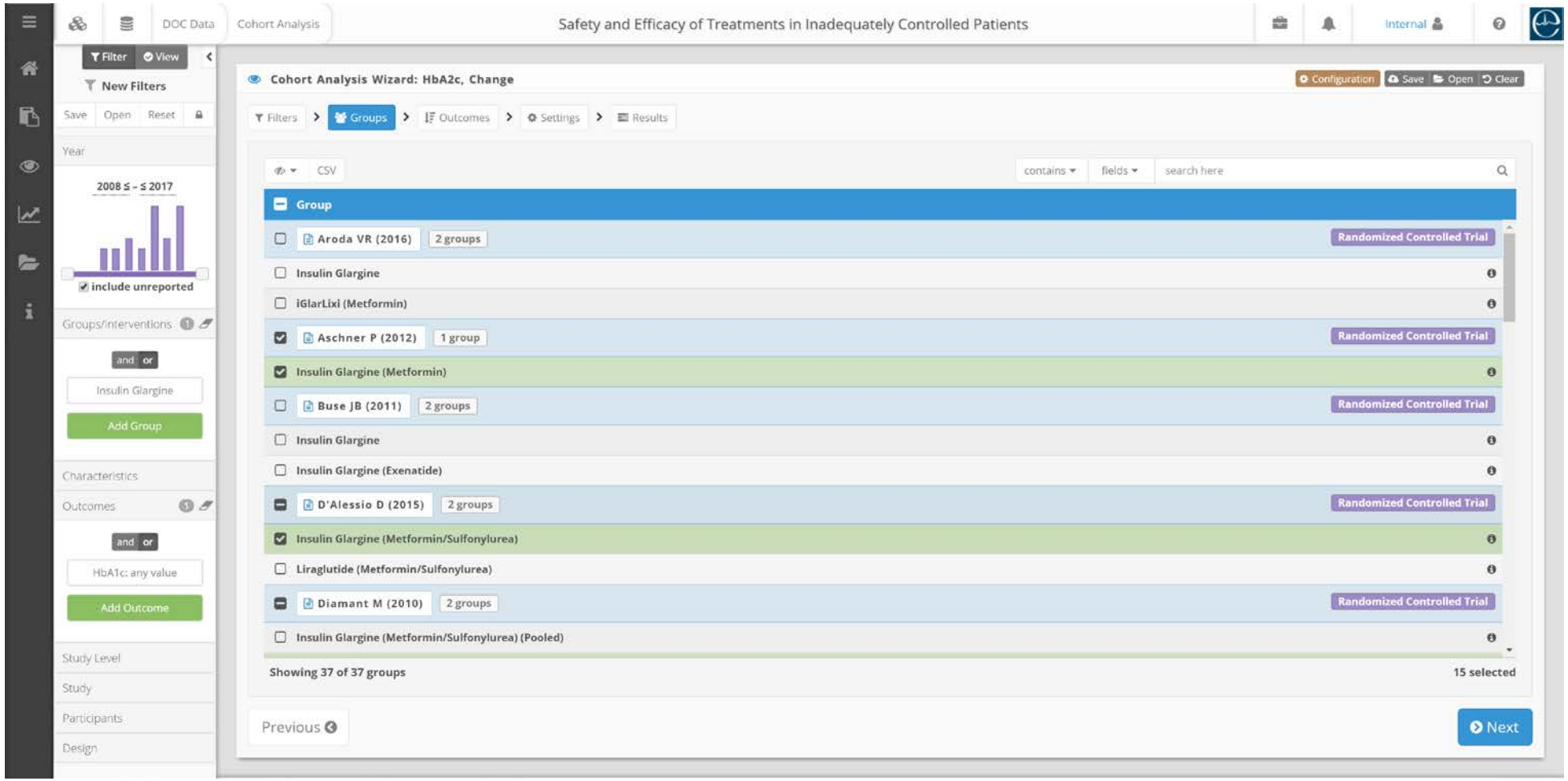
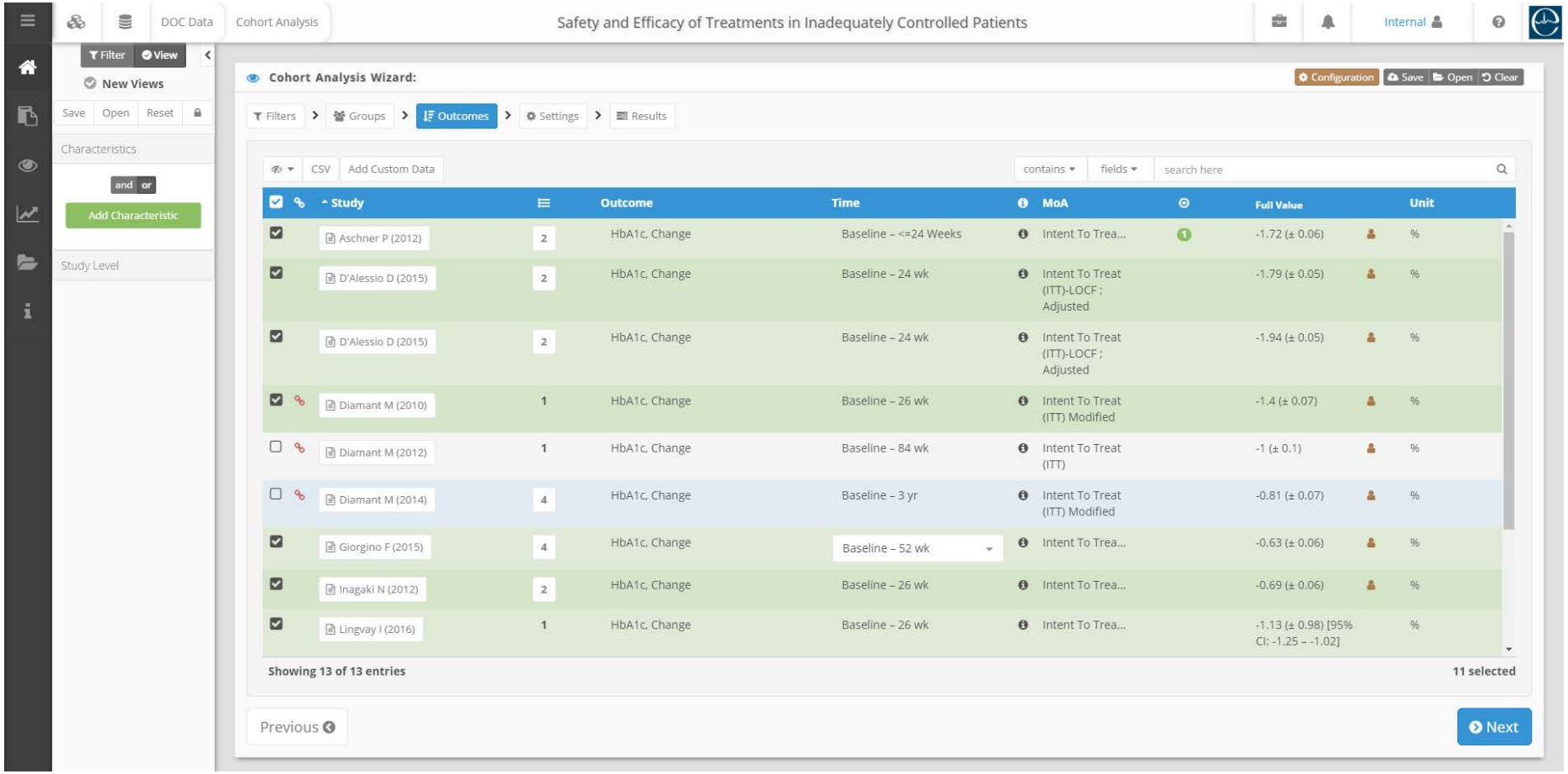
Cohort Analysis – Groups

Does Insulin Glargine Reduce HbA1c?



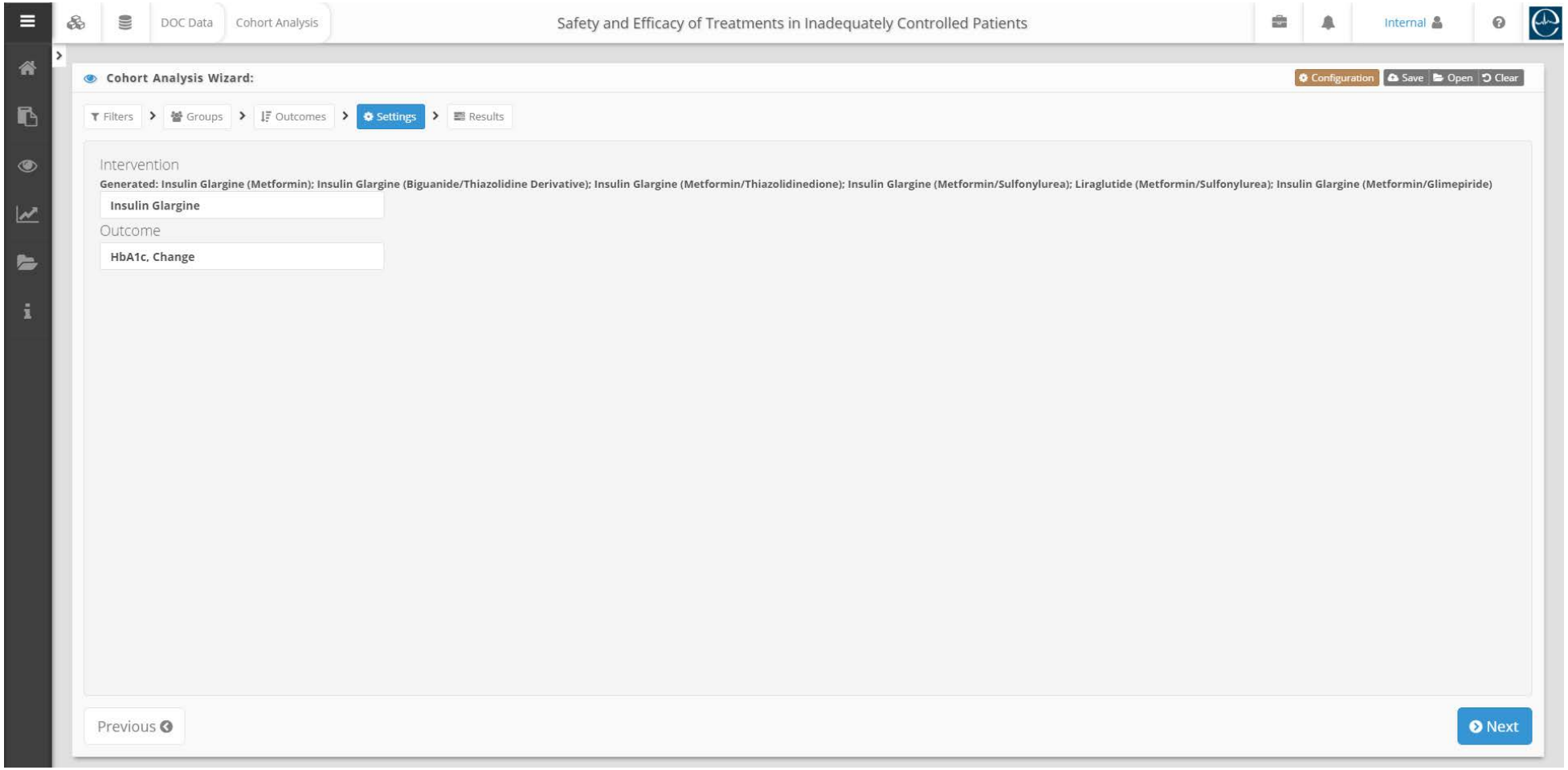
Cohort Analysis – Outcomes

Does Insulin Glargine Reduce HbA1c?



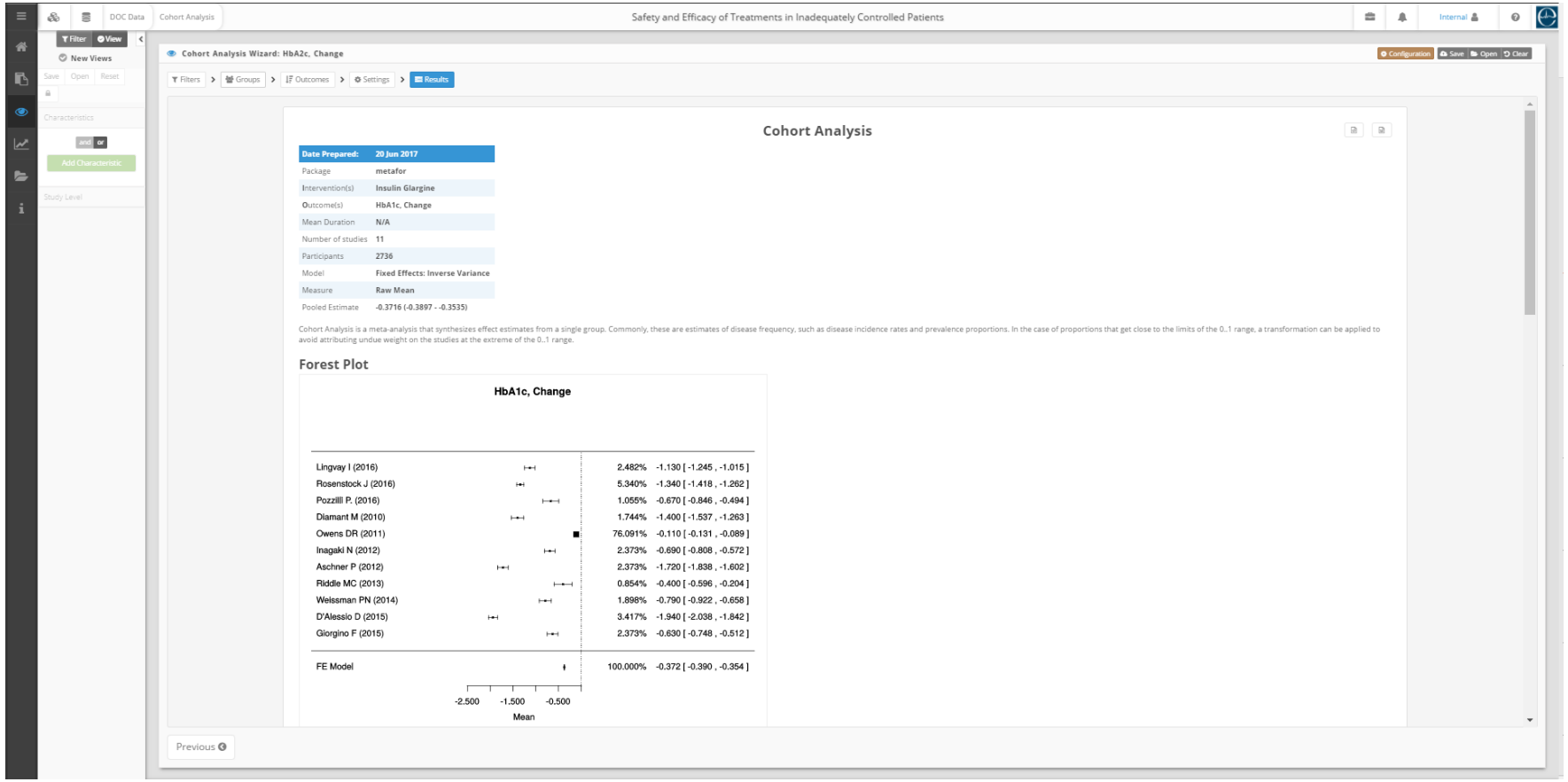
Cohort Analysis – Settings

Does Insulin Glargine Reduce HbA1c?



Cohort Analysis – Results

Does Insulin Glargine Reduce HbA1c?



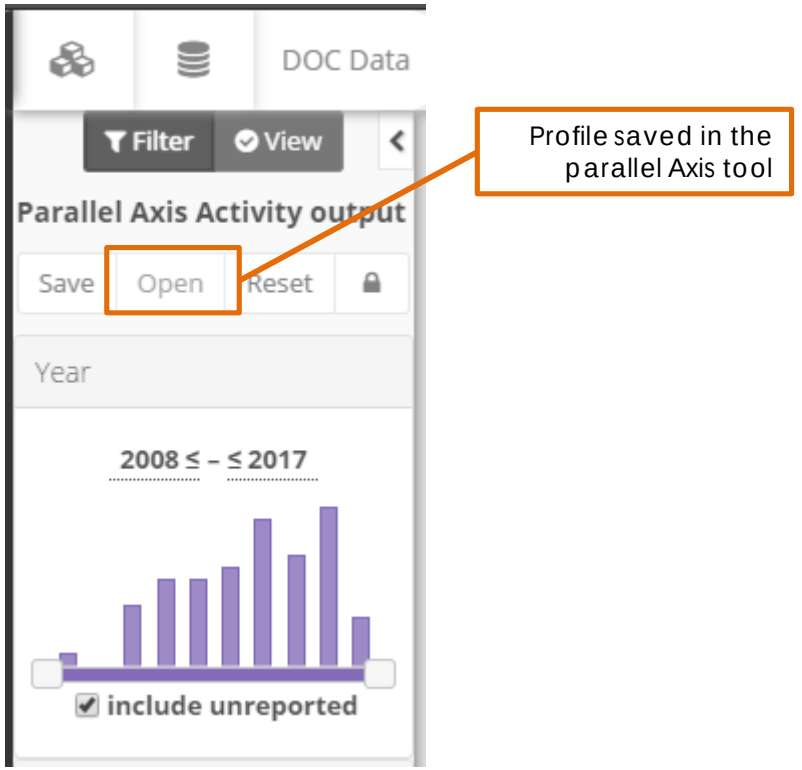
Independent Activity:
Cohort Analysis

Cohort Analysis INDEPENDENT ACTIVITY

Does Insulin Glargine reduce weight for patients with following profile?

- **Age, >= 50**
- **BMI, <= 35**
- **Race, Caucasian, >= 70%**
- **Gender Female, 40% to 60%**

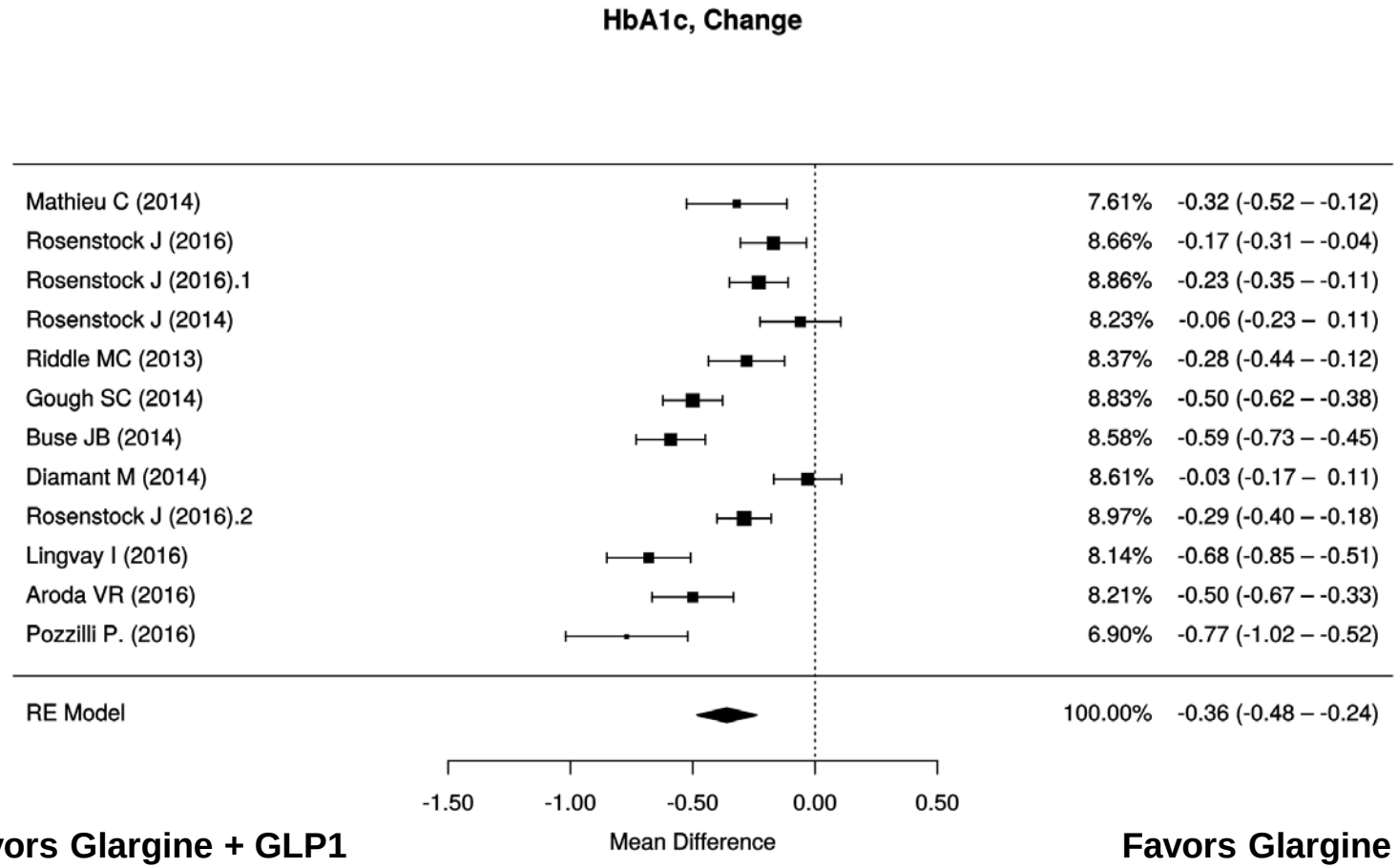
Clue



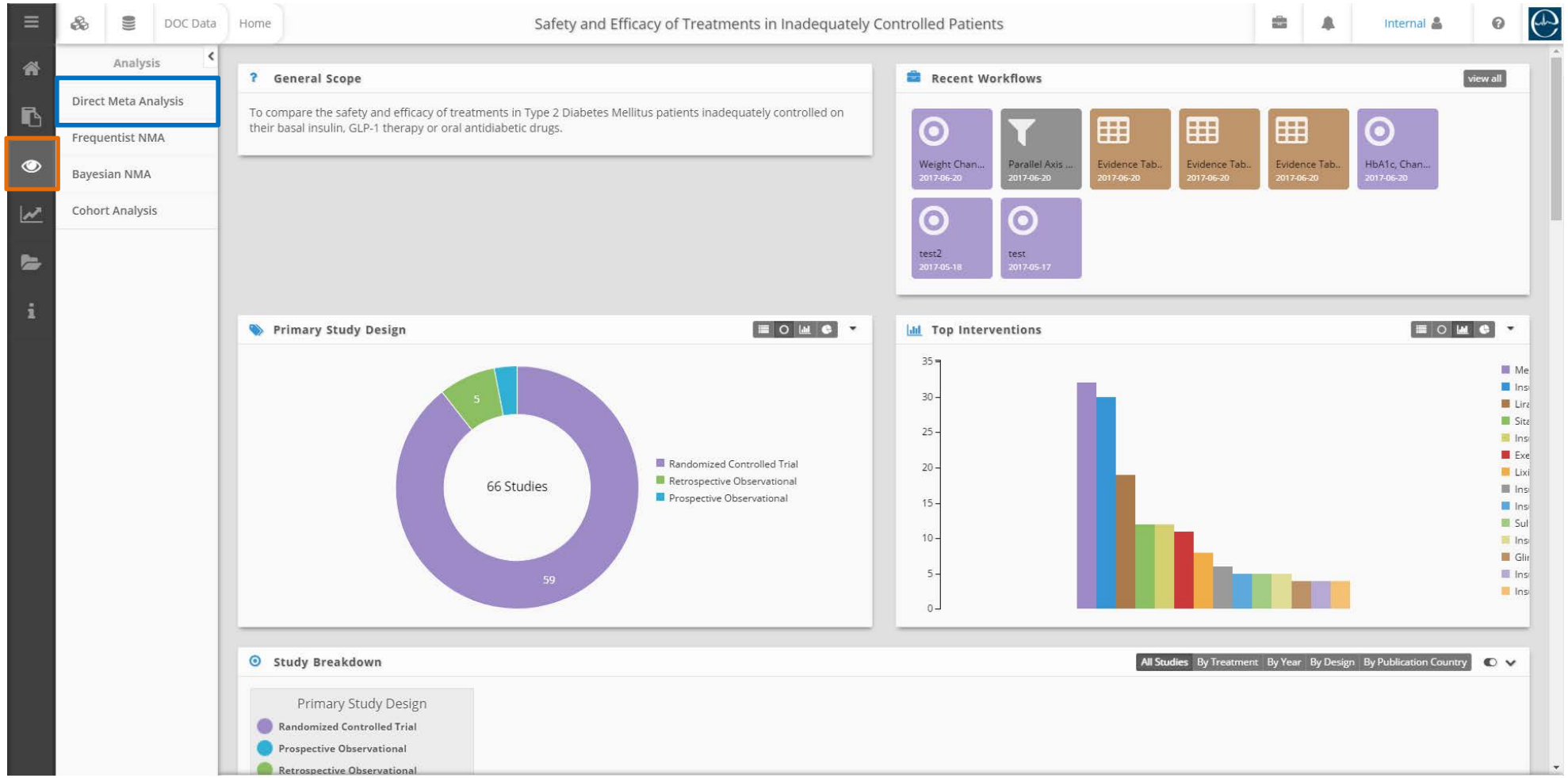
DOC Data:
Direct Meta-Analysis

Direct Meta-Analysis

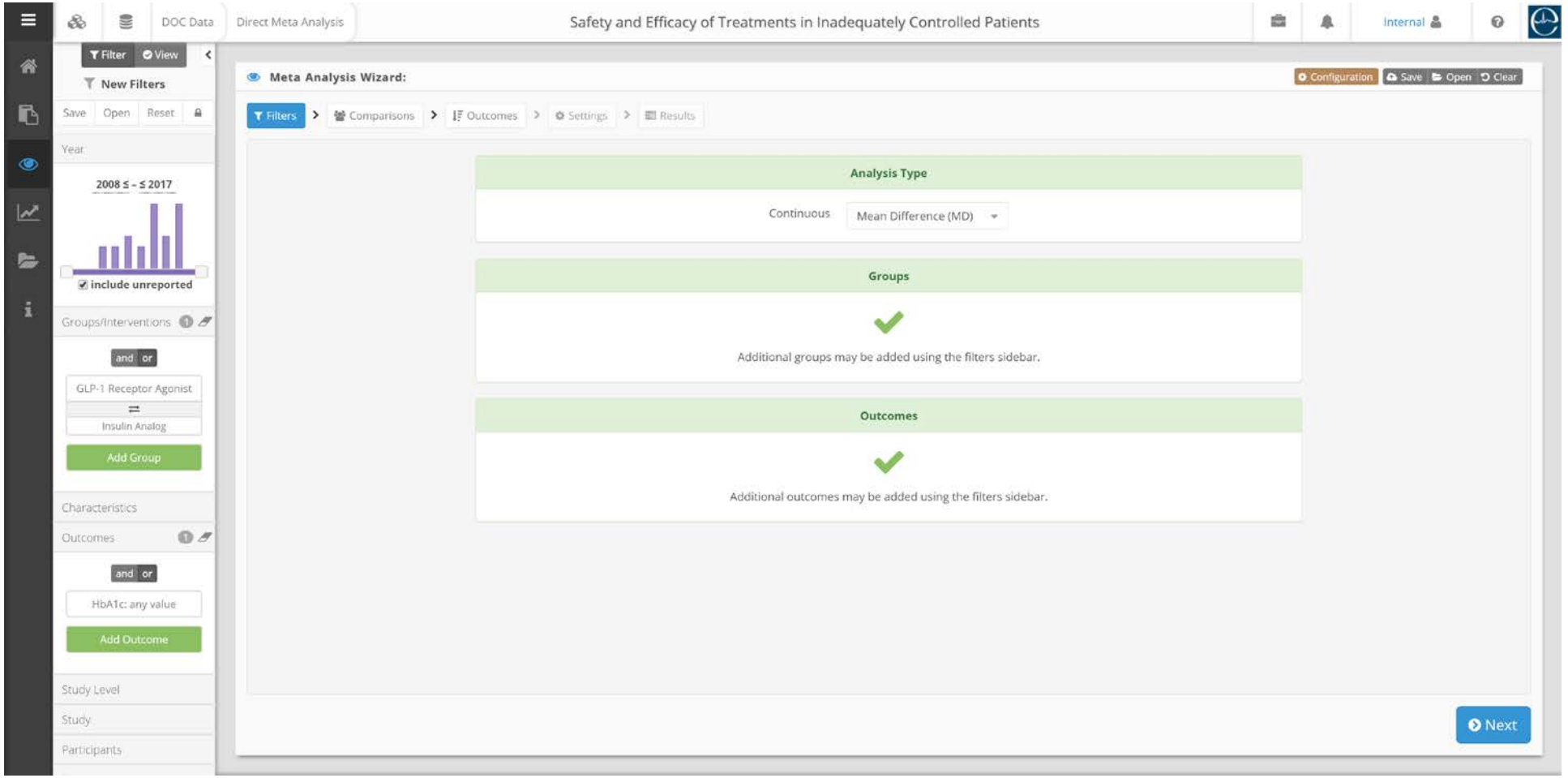
Comparative analysis, Glargine+GLP1 vs Glargine for reduction of HbA1c?



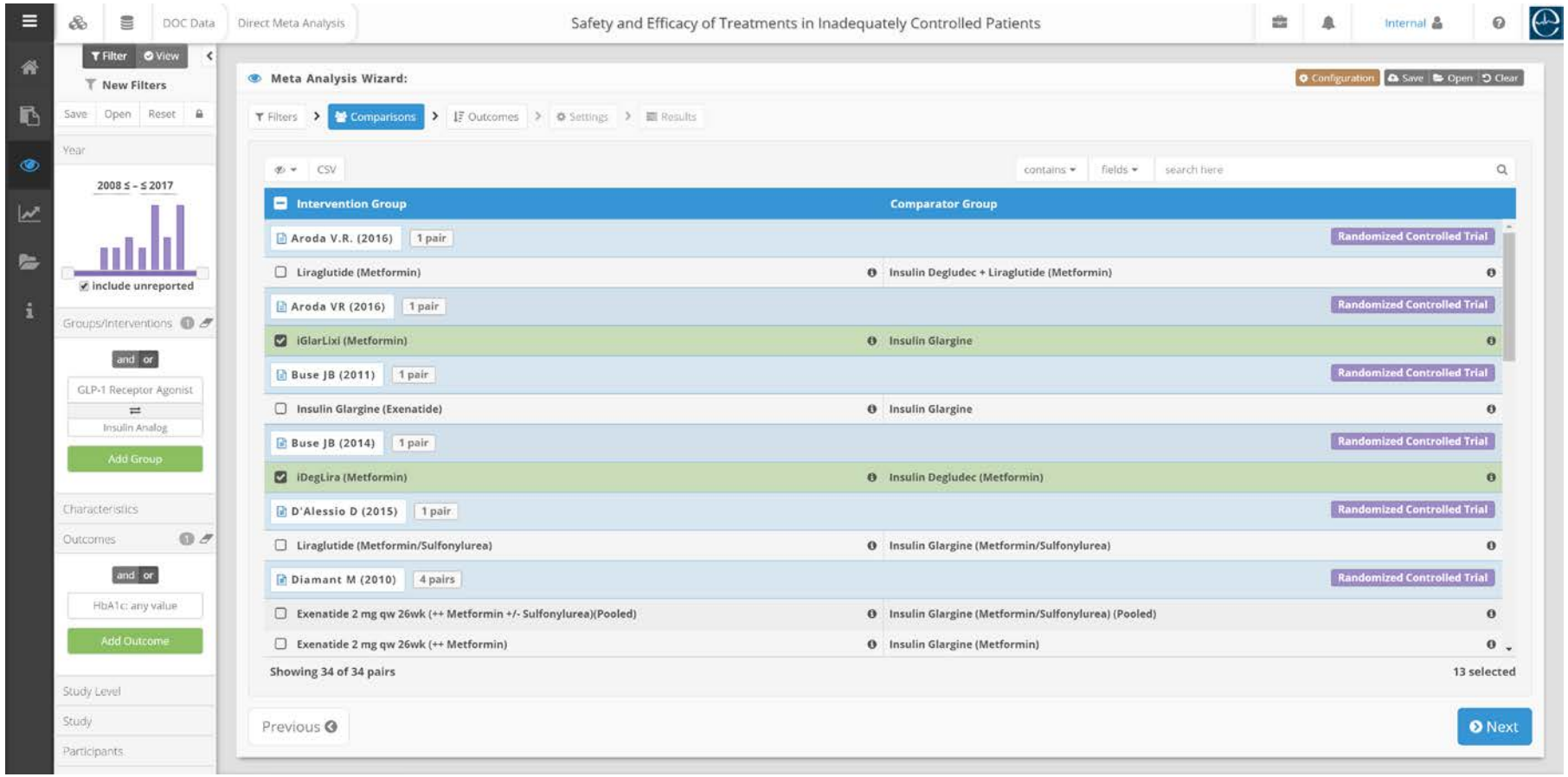
Direct Meta-Analysis – Demo



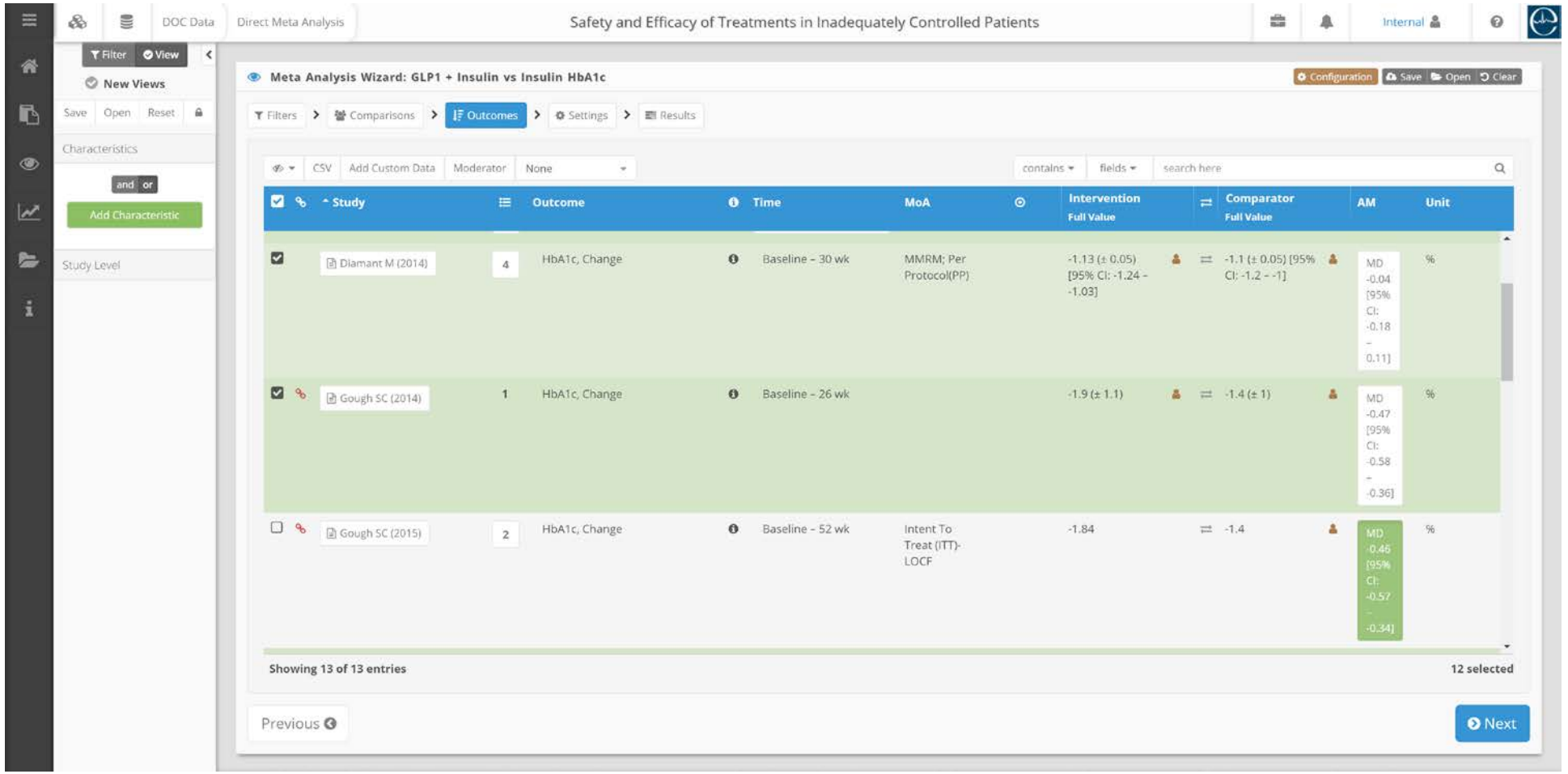
Direct Meta-Analysis – Demo



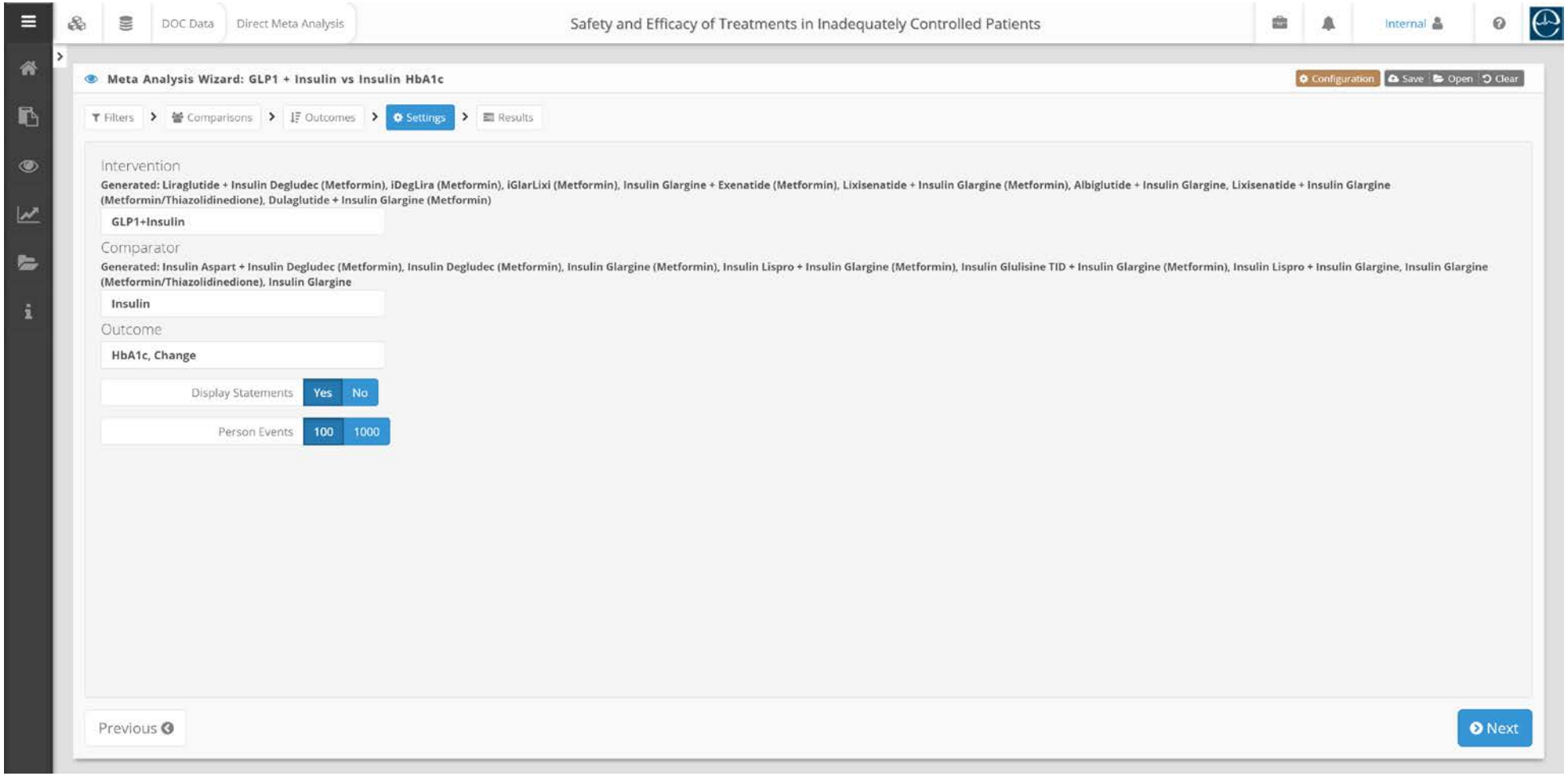
Direct Meta-Analysis – Demo



Direct Meta-Analysis – Demo



Direct Meta-Analysis – Demo



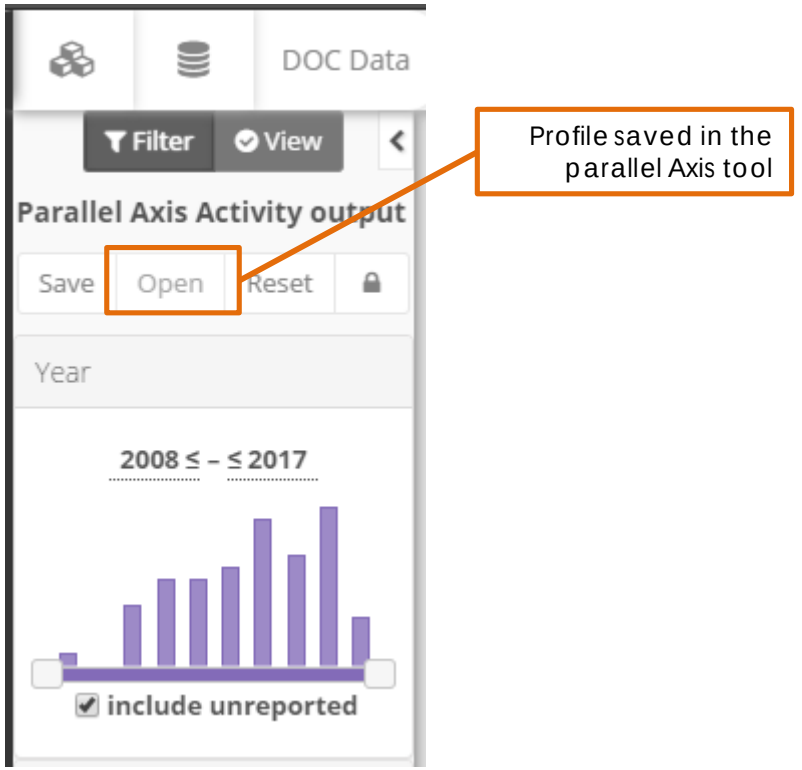
Independent Activity:
Direct Meta-Analysis

Direct Meta-Analysis INDEPENDENT ACTIVITY

Comparative analysis, Glargine+GLP1 vs Glargine for change in weight?

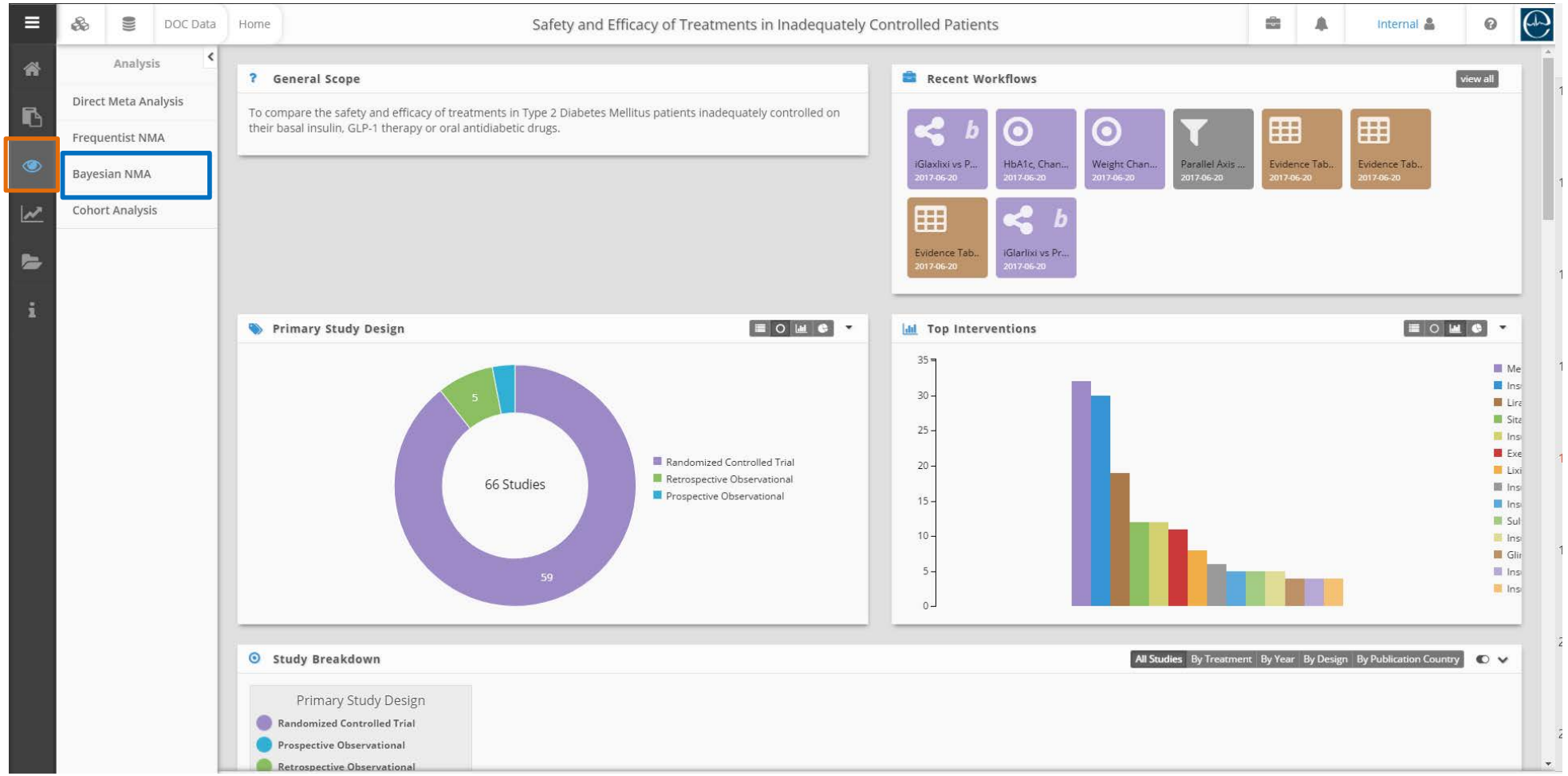
- Age, >= 50
- BMI, <= 35
- Race, Caucasian, >= 70%
- Gender Female, 40% to 60%

Clue



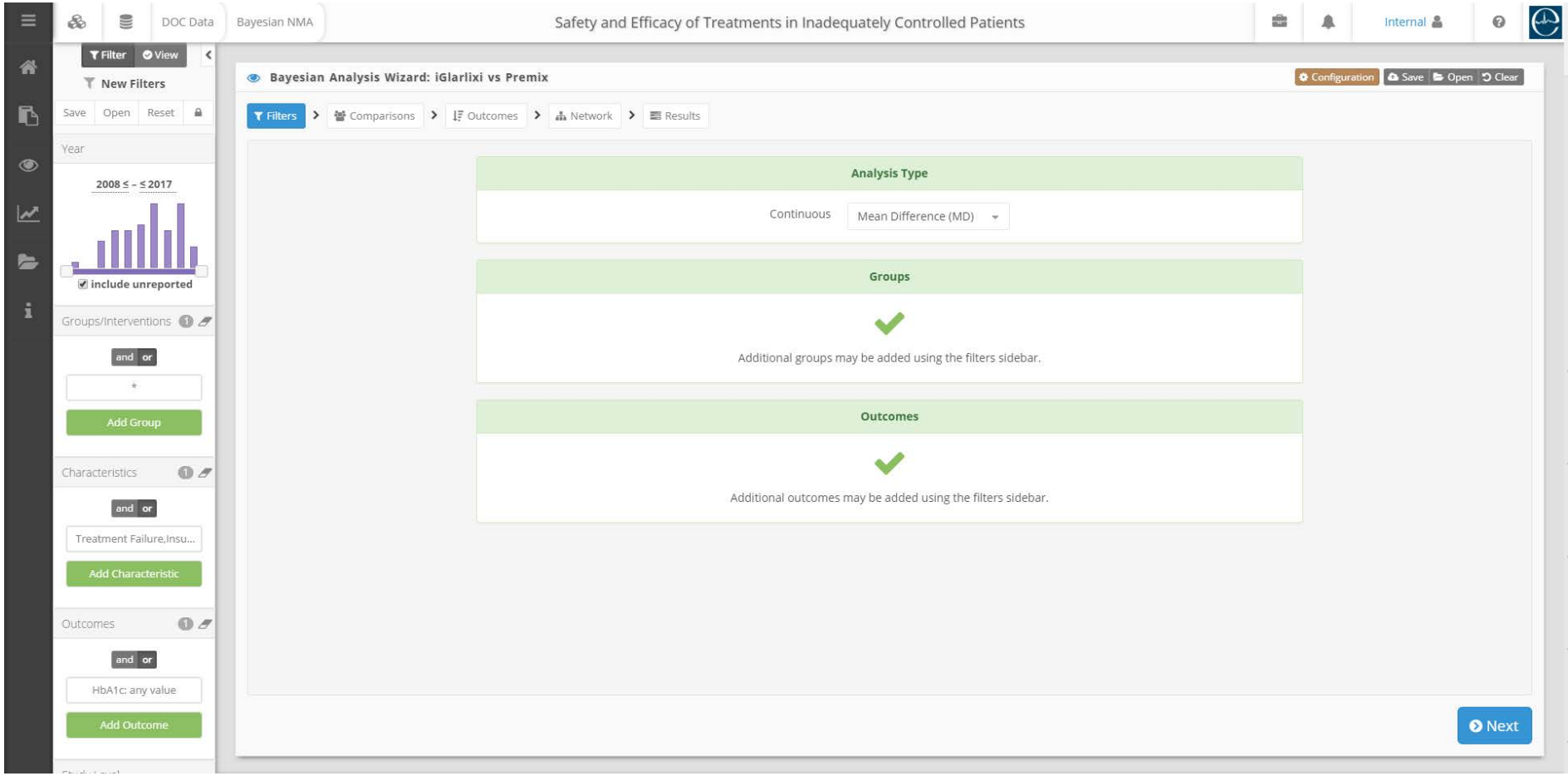
DOC Data:
Bayesian Network Meta-Analysis

Bayesian NMA – Demo



Bayesian NMA

What is the comparative reduction of HbA1c, with iGlarlixi vs Premix, in patients who failed insulin?



Bayesian NMA

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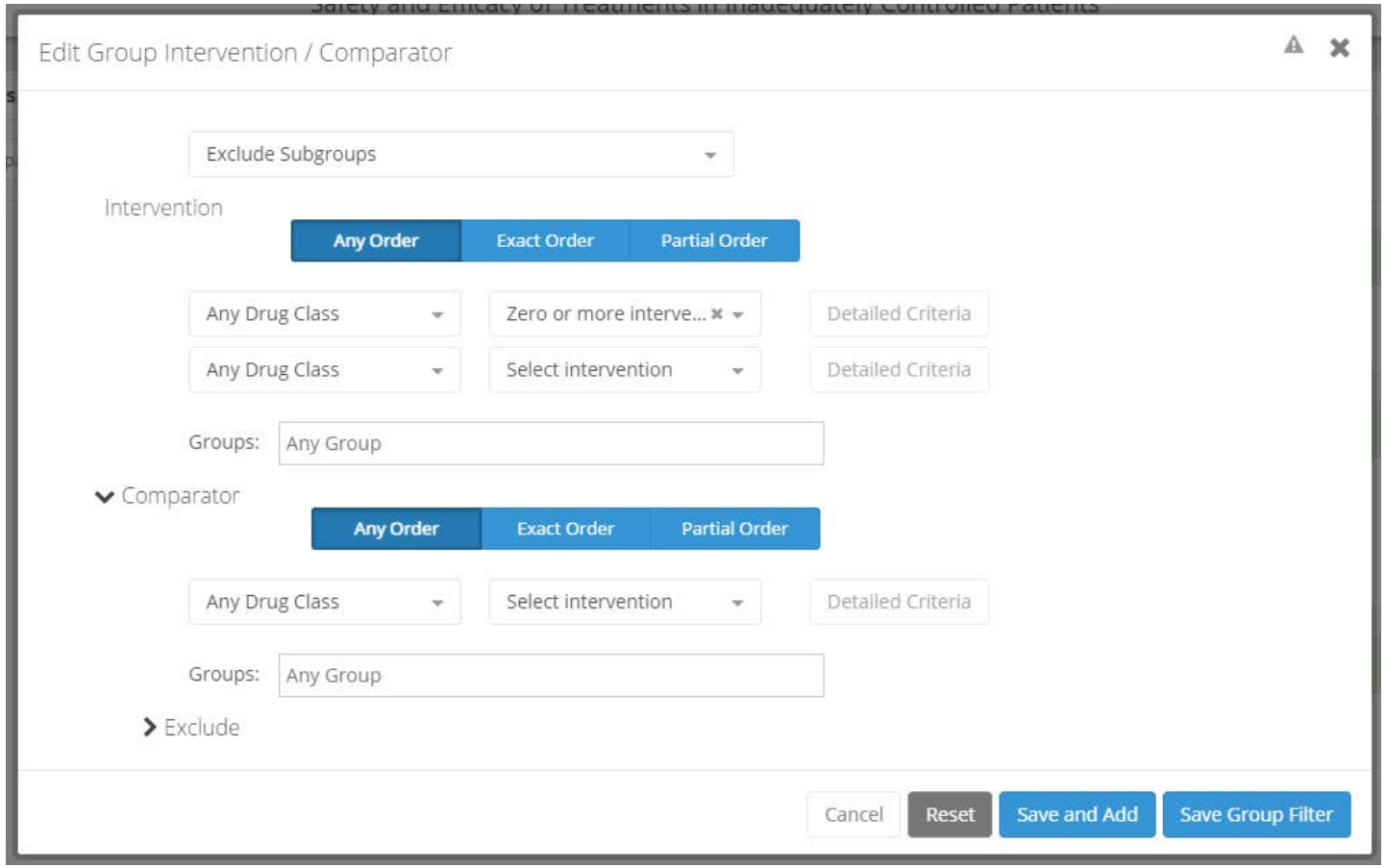
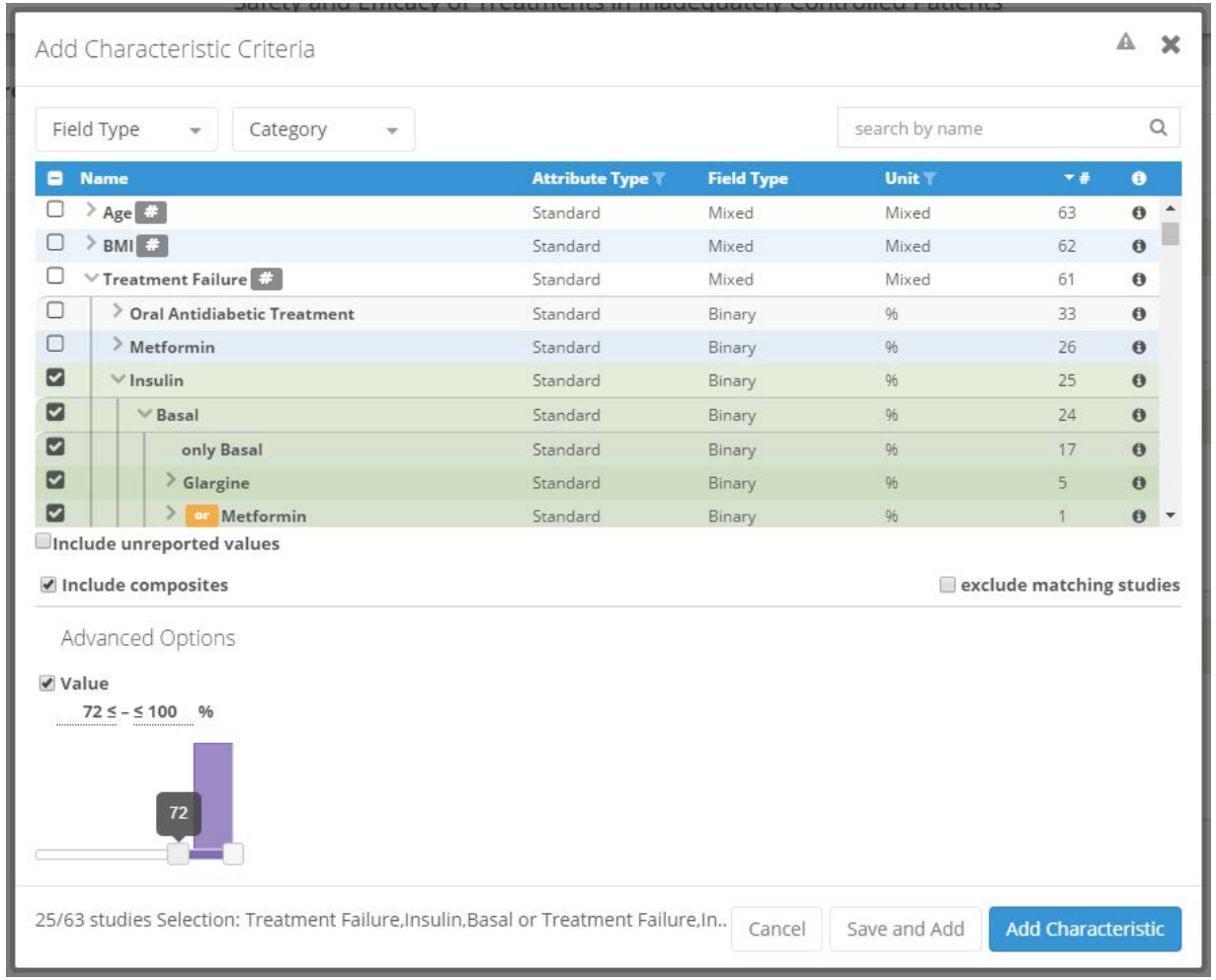


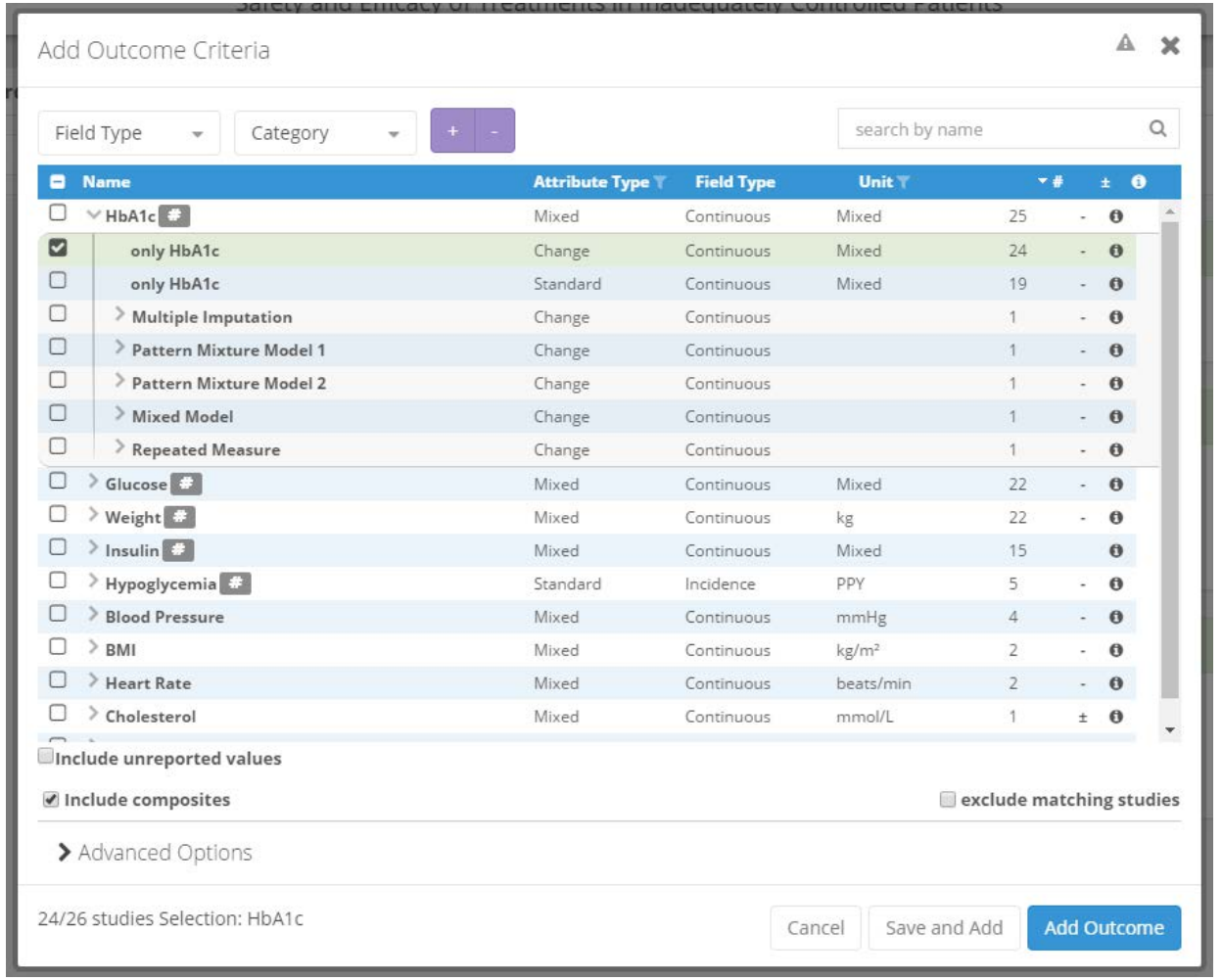
Bayesian NMA

What is the comparative reduction of HbA1c, with iGlarlixi vs Premix, in patients who failed insulin?



Bayesian NMA

What is the comparative reduction of HbA1c, with iGlarlixi vs Premix, in patients who failed insulin?



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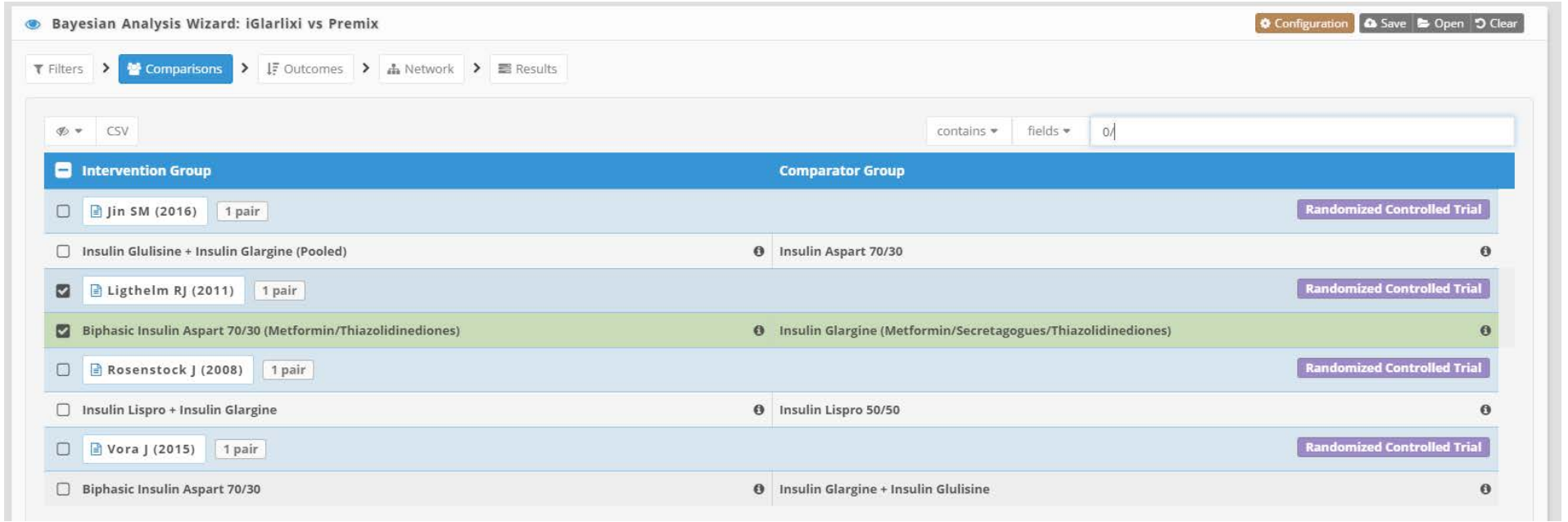

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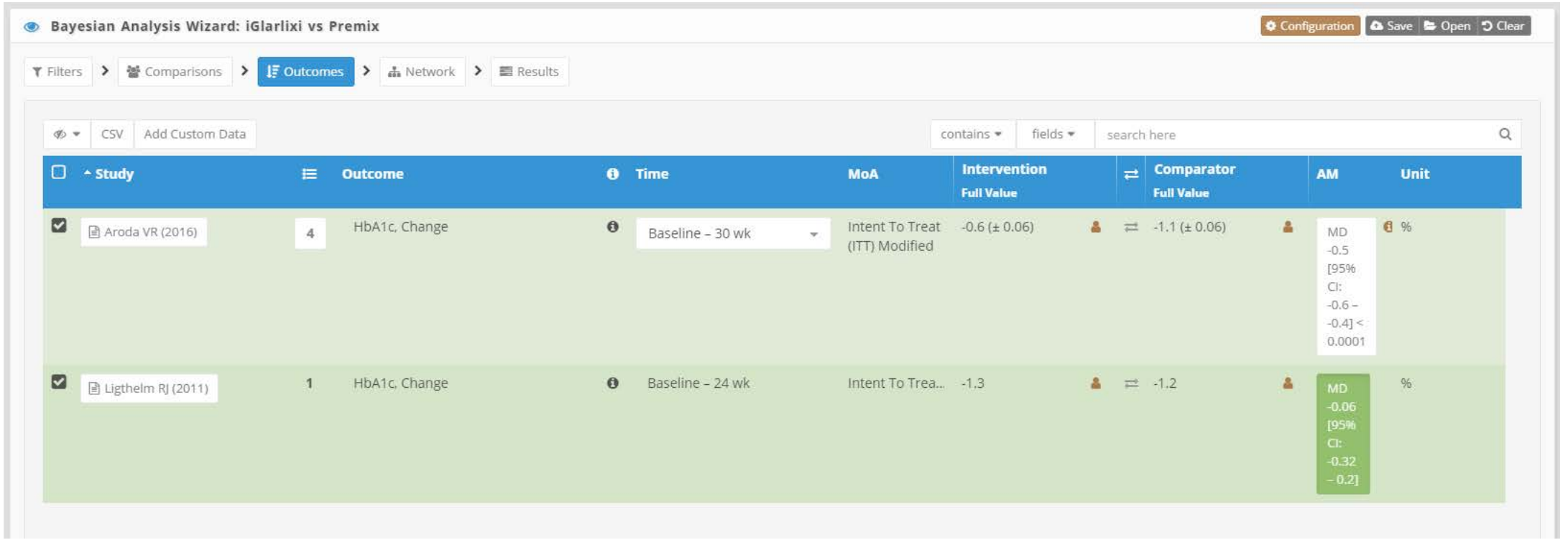

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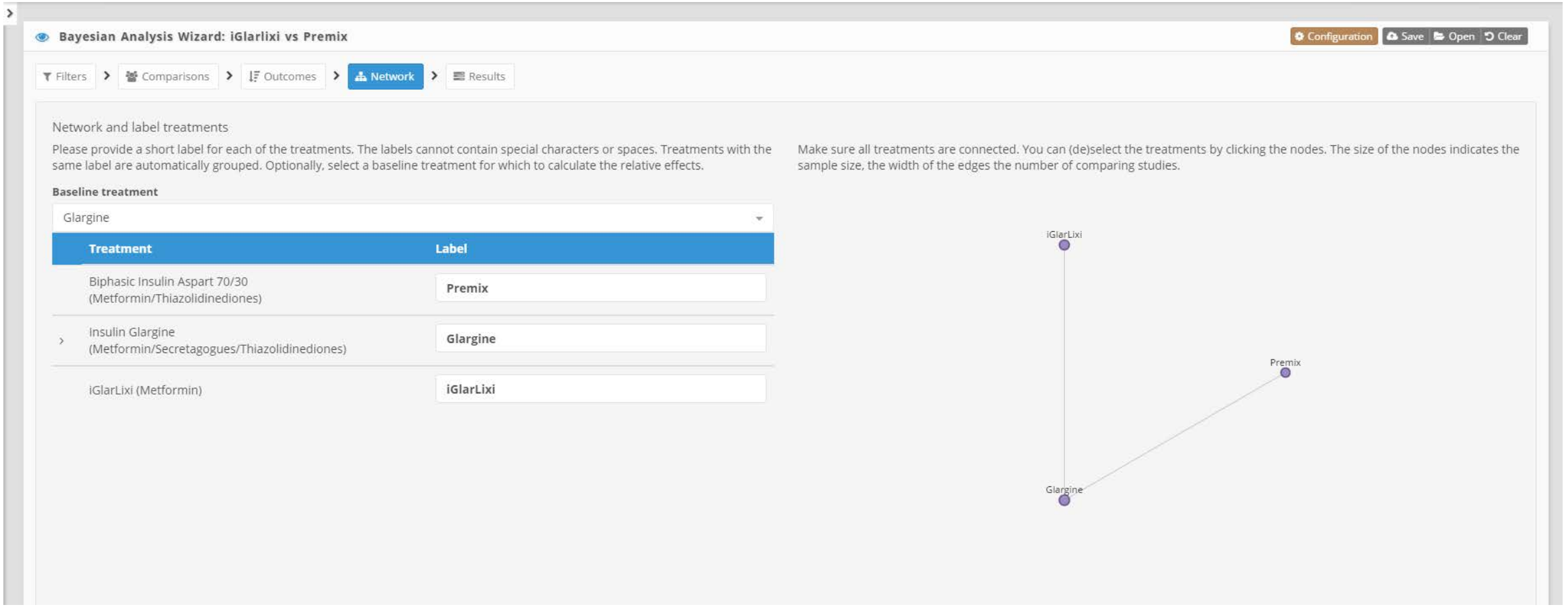

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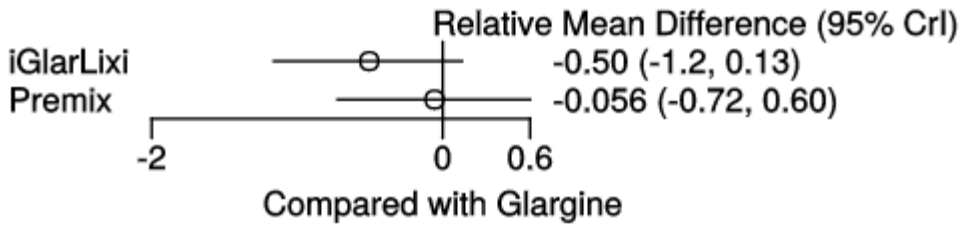


The table below gives the cumulative probabilities of the ranks per treatment

	Rank 1	Rank 2	Rank 3
Glargine	0.022	0.43	1
iGlarLixi	0.86	0.96	1
Premix	0.11	0.6	1

Independent Activity:
Direct Meta-Analysis

Direct Meta-Analysis

What is the efficacy of Glatiramer Acetate in treatment of Multiple Sclerosis based on a relapse outcome?

P	Patients with Relapsing-Remitting Multiple Sclerosis
I	Glatiramer Acetate
C	Placebo
O	# of patients who have relapses during follow-up

Independent Activity:
Bayesian NMA

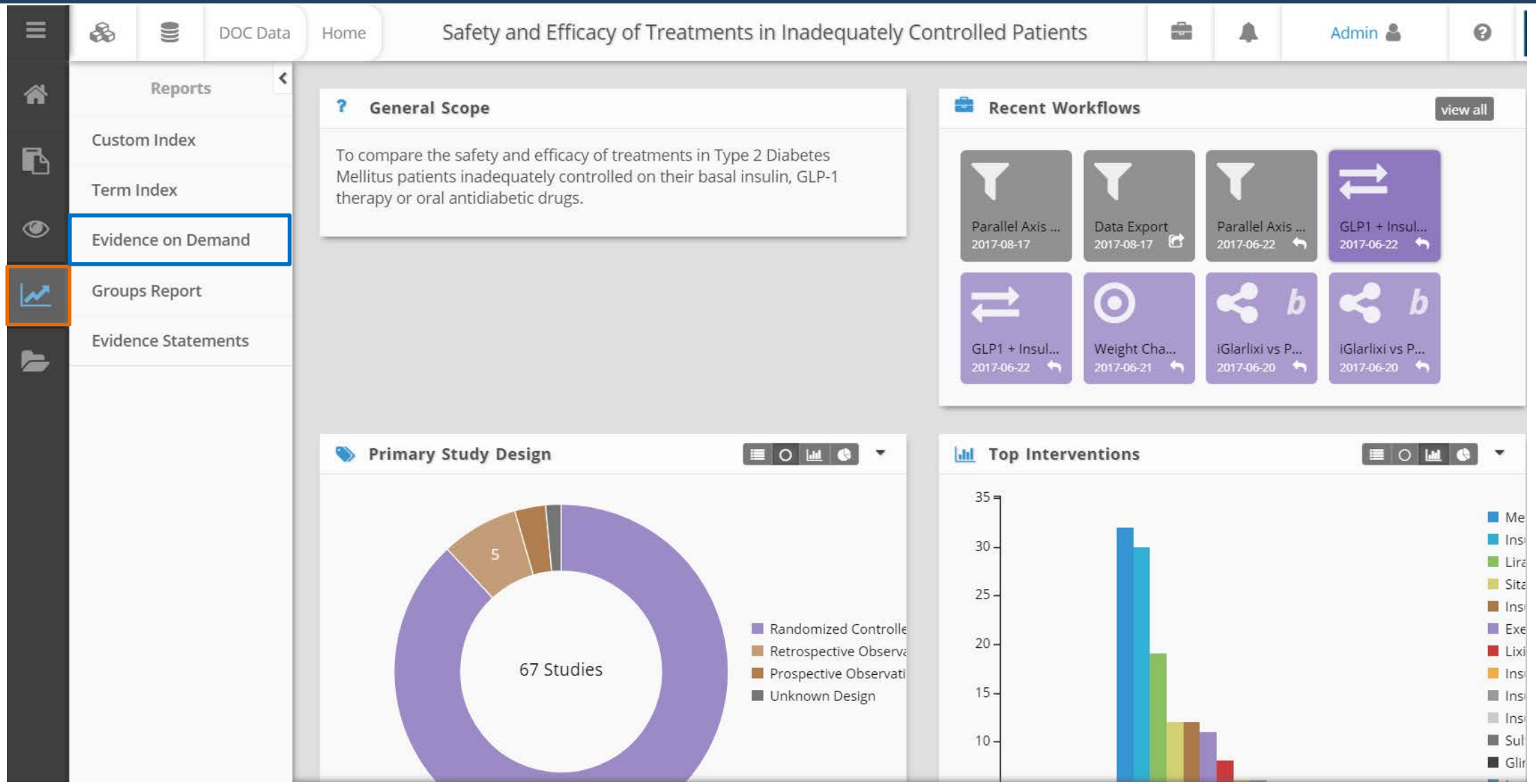
Direct Meta-Analysis

What is the comparative efficacy of non-antibody interventions in treatment of Multiple Sclerosis based on relapse outcome?

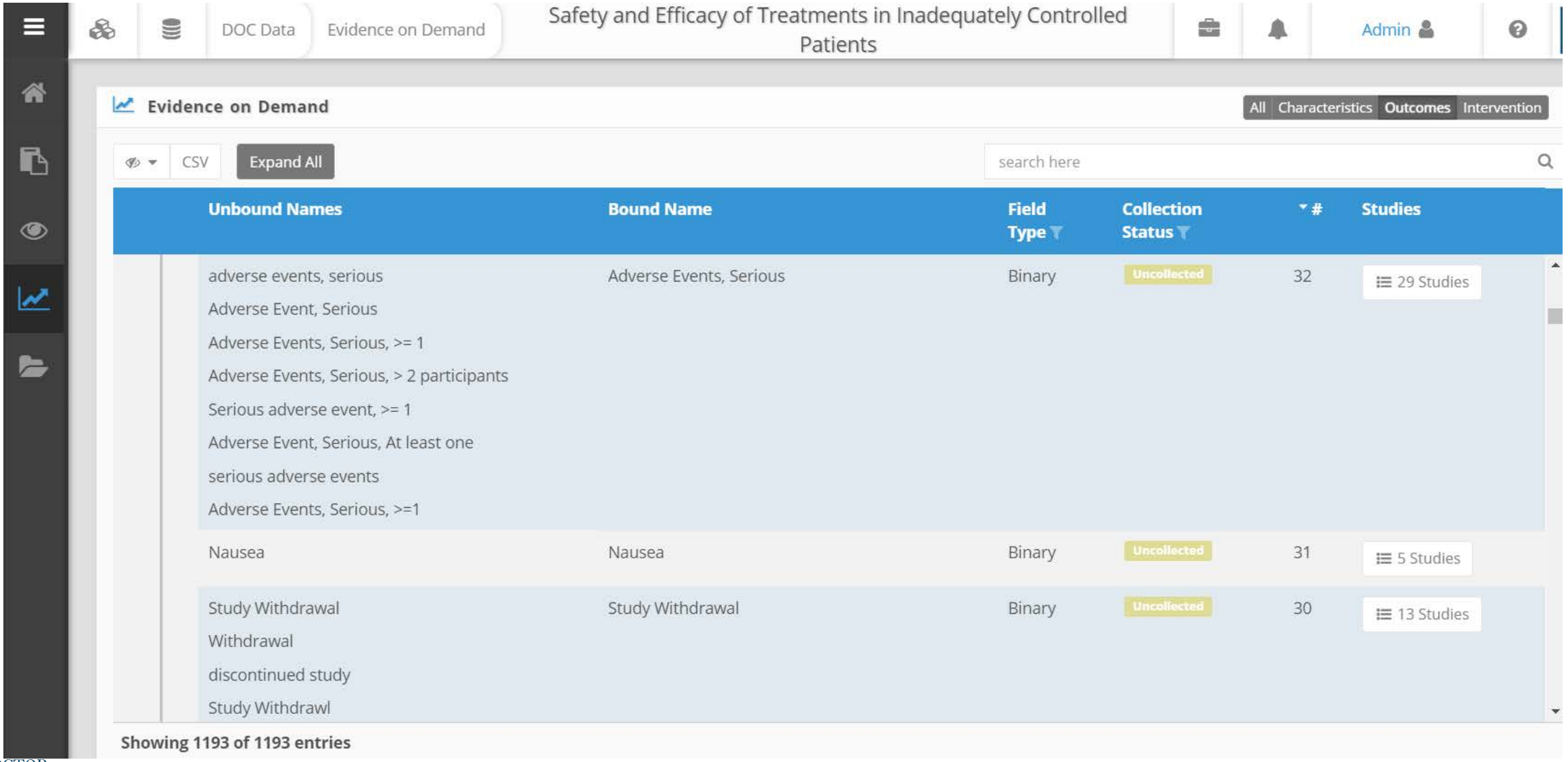
- **P:** Patients with Relapsing-Remitting Multiple Sclerosis
- **I:** Non-antibody interventions
  - Dimethyl Fumarate
  - Fingolimod
  - Glatiramer Acetate
  - Interferon Beta 1a
  - Interferon Beta-1b
  - Peginterferon Beta-1a
  - Teriflunomide
- **C:** All Interventions and Placebo
- **O:** # of patients who have relapses during follow-up

DOC Data:
Evidence on Demand

Evidence on Demand – Demo



Evidence on Demand – Demo



DOC Data:
Exploring Heterogeneity

Tools for Assessing Heterogeneity

- **Evidence Table Wizard**
- **Data Export Wizard**
- **Parallel Axis Chart**
- **Cohort Analysis**

DOC Data:
Analytic Sensitivity Dashboard

Analytic Sensitivity Dashboard

See all variations of possible analyses

Sorted by Comparisons & Outcomes,

View graphical representations of studies OR

Click into different analyses to confirm selections and run!

Analytics Report

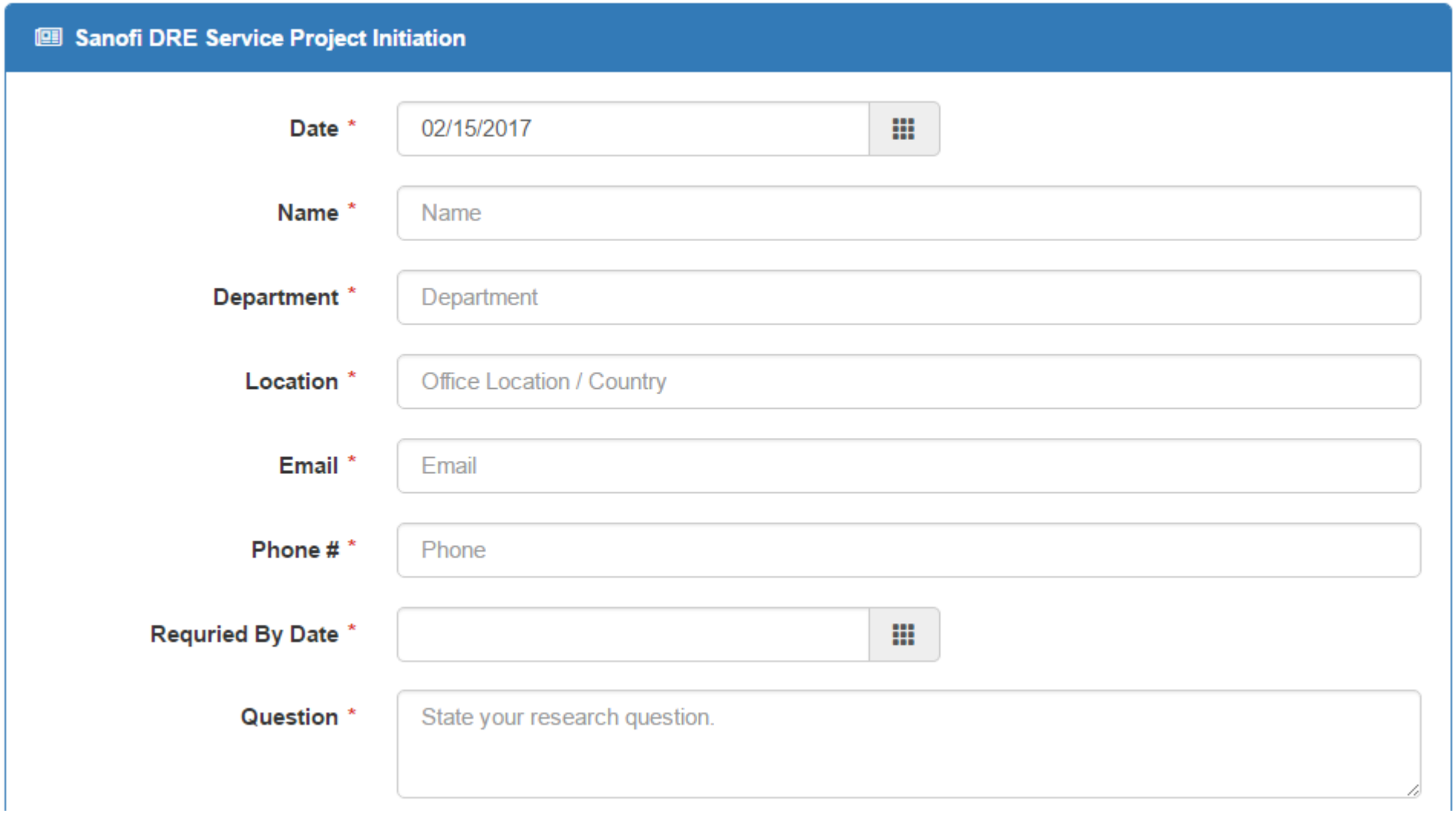
Group Interventions	Group Comparators	Comparisons	Direct Meta Analyses	Bayesian Analyses	Frequentist Analyses	Cohort Analyses	Studies
> Insulin, Glargine + Insulin, Lispro or Insulin, Aspart or Insulin, Insulin Glulisine	Insulin, Glargine + Insulin, Lispro or Insulin, Aspart or Insulin, Insulin Glulisine	2					
> Insulin, Lispro + Insulin, Glargine	Insulin, Lispro, Mix 50 + Insulin, Lispro, Mix 25	2					
v Insulin, Glargine	Non-Glargine Insulin	46					
v Cancer			13	13	13	4	8 Studies
Breast			5	5	5	0	6 Studies
Breast			5	5	5	0	3 Studies
Breast			3	3	3	4	2 Studies
> Insulin			0	0	0	7	1 Study

DOCTOR EVIDENCE "Turning data into knowledge"

Initiating a Project

Requesting a Customized Library Package

https://reports.doctorevidence.com/pages/Client/ServiceProject.aspx



Initiating a Project – Additional Contact Info

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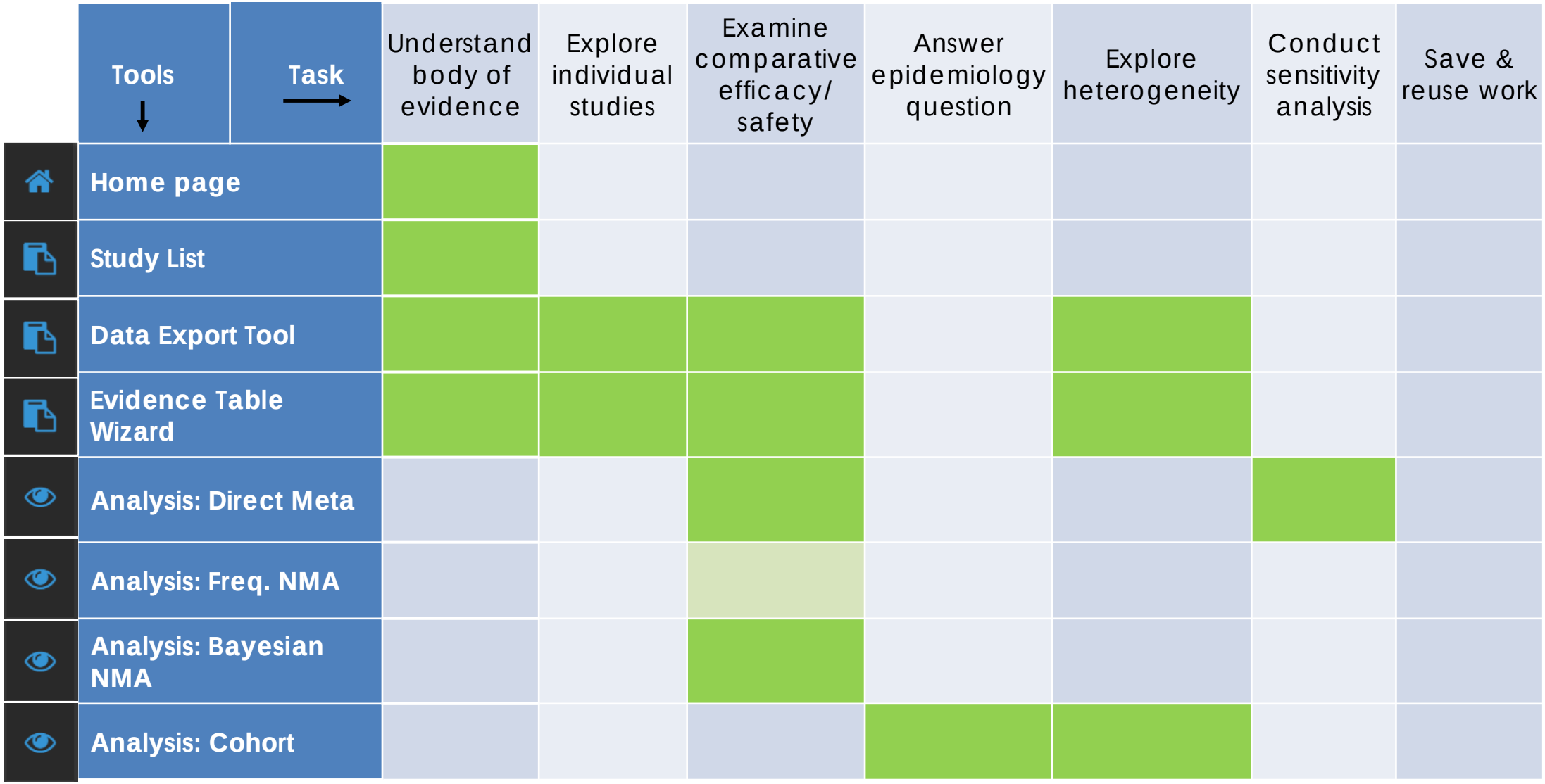
DOC Data: Task-Tool Matrix



Tools ↓ / Task →	Understand body of evidence	Explore individual studies	Examine comparative efficacy/ safety	Answer epidemiology question	Explore heterogeneity	Conduct sensitivity analysis	Save & reuse work
Home page	■						
Study List	■						
Data Export Tool	■	■	■		■		
Evidence Table Wizard	■	■	■		■		
Analysis: Direct Meta			■			■	
Analysis: Freq. NMA							
Analysis: Bayesian NMA			■				
Analysis: Cohort				■	■		

DOCTOR EVIDENCE
"Turning data into knowledge"

DOC Data: Task-Tool Matrix