Clinical Trial Feasibility: a real world analysis

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Clinical trial feasibility

- Clinical trials are expensive, time consuming and can result in cancelled trials and can have costly amendments.
- Using a data-driven approach for feasibility allows for an overall understanding of the population of interest and characteristics of the population by examining inclusion/exclusion criteria for the population of interest.
- By enabling the CDM, and OHDSI tools we are able to mimic protocol populations using observational data to better understand how inclusion/exclusion criteria affect the population in a timely, concise and reproducible manner.

Using OHDSI tools to conduct clinical trial feasibility

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ABSTRACT

Background: Observational data has been used in support of various epidemiological studies including safety surveillance, cohort characterization and outcomes research. A novel use of observational data that is enabled through the use of OHDSI tools in assessing clinical trial feasibility.

Methods: Using the tools from the OHDSI network we are able to apply standard methods to effectively assess inclusion criteria for a potential clinical trial population. A case study example has been executed to illustrate feasibility.

Results: The result of using observational data has provided efficiencies in protocol design, the ability to address operational questions and possibly avoid protocol amendments. The case study illustrates the ability to adequately simulate 7 out of 9 criteria and provide insights around selected criteria.

Conclusion: Insights gained by protocol simulation can be adapted to enhance how clinical trials are designed and conducted. By using the common data model, standard vocabularies and OHDSI tools we are able to deliver results in a standard, concise, timely and reproducible manner.

BACKGROUND

- The use of observational data in retrospective analyses have been thoroughly explored and studied. Applying this data in the use of clinical trial feasibility has been a new application of the data[1].
- By utilizing the OMOP common data model (OMOP CDM) and the current OHDSI tools, the ability to utilize the data in clinical trial feasibility is possible and can address operational questions, provide insight in overall population eligibility, impact protocol design, and possibly avoid protocol amendments for a clinical trial.

METHODS

- Typical clinical trial feasibility lifecycle (Figure 1.)

  1.) Eligible protocols are identified in therapeutic areas that are of interest to the organization throughout the clinical trial lifecycle from trial design through active trials facing recruitment challenges. Additionally, review of inclusion/exclusion criteria that can be addressed through the data elements available in the CDM data.

  2.) Creation of concept sets and/or utilization of concept sets from standard vocabularies in ATLAS to describe the criteria set.

  3.) Each criteria of interest is applied to the index population (or inclusion criteria) in ATLAS.

  4.) The individual match percentages for each criteria and overall match criteria are evaluated for each protocol.

  5.) Results are shared with clinical team.
- A case study for a major depressive disorder (MDD) protocol has been entered through the process and results generated and evaluated; Inclusion and exclusion criteria are shown in Figure 2 from clinicaltrials.gov.
- The index population was defined as people having a condition occurrence of a primary condition of MDD in the 2014 calendar year between the ages of 21 and 64 and with least 180 days prior. All people matching those criteria must also have no diagnosis of hypothyroidism between 90 days before and including the index. The latest event of MDD for each patient is the index date used in evaluation.

Figure 1. Lifecycle of clinical trial feasibility

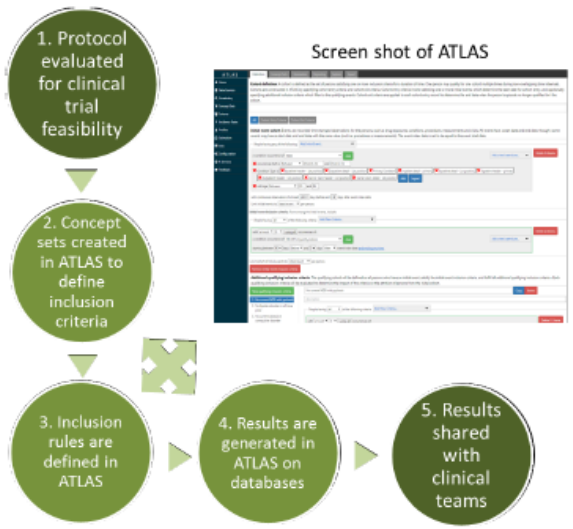

Figure 2. MDD protocol from clinicaltrials.gov[3]

RESULTS

- In less than 9 months, the team has used ATLAS to answer over 20+ protocols/programs with regard to various criteria including assessing the impact of individual protocol criteria, operational questions pertaining to cohort selection and population characteristics prior to drafting protocols.
- The types of insights gained by various protocols are: insights of inclusion criteria, assessing impact of changing criteria, and checking for adequate match rates amongst the population found in the retrospective observational data cohort.
- Of the 4 inclusion criteria in the case study, 2 can be adequately be addressed in the tools. Of the 5 exclusion criteria, 5 can be simulated in observational data.
- The overall match rate for this population is 56.60% based on the criteria entered (Table 1) and individual match criteria are displayed in Table 2 for the Truven CCAE database (a large US commercially insured claims database)
- The criteria that have lower than a 90% match rate were: no bipolar disorder in all time prior, no more than 3 previous antidepressants in all time prior.

Table 1. Summary of index population and match percentage

	Match rate	N	Index population
Summary Statistics	56.60%	180,513	318,950

Table 2. Inclusion criteria from MDD protocol simulation

Inclusion Rule	N	% Satisfied	% To-Gain
No current MDD with pychosis	309,510	97.04%	1.31%
No bipolar disorder in all time prior	282,586	88.60%	5.60%
No current obsessive compulsive disorder	318,520	99.87%	0.07%
No current borderline personality disorder	316,888	99.35%	0.19%
No current eating disorder	314,022	98.45%	0.80%
No schizophrenia in all time prior	315,981	99.07%	0.21%
No substance abuse diagnosis 6 months prior to index	302,983	94.99%	2.39%
No diagnosis of suicidal ideation in past 365 days	318,342	99.81%	0.04%
No more than 3 previous antidepressants in all time prior	227,315	71.27%	22.16%
No antidepressant use greater than 1825 days (60 months) all time prior	310,340	97.30%	1.69%

CONCLUSIONS

- The ability to analyze clinical trial feasibility thorough observational data may provide substantial insights in avoiding amendments, recruitment challenges and protocol design.
- By utilizing the common data model across various databases, the analysis to be simulated in different populations and geographies which can be representable of recruitment regions.
- The OHDSI tools can facilitate many assumptions in a protocol for clinical trial feasibility a priori which is a valuable proposition. The tools provide a strong framework to conduct the analysis in a standardized and reproducible manner.

REFERENCES

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2. Janssen Research & Development, LLC. An Efficacy and Safety Study of Sirukumab in Participants With Major Depressive Disorder. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2016 Sep 10]. Available from: http://clinicaltrials.gov/show/NCT02473289 NLM Identifier: NCT02473289.

CONFLICT OF INTEREST STATEMENT

Rupa Makadia, Jamie Forlenza, Frank DeFalco, Chris Knoll, and Patrick Ryan are full time employees of Janssen Research and Development, a unit of Johnson and Johnson. The work on this study was part of their employment. They also hold pension rights from the company and own stock and stock options.

Background

- Clinical trial feasibility analyses address operational questions, provide insight in overall population eligibility, impact protocol design, and can potentially avoid protocol amendments for a clinical trial. At Janssen this utility is provided to clinical teams by identifying appropriate protocols and pre-protocol documents that may be studied using observational data (mainly claims databases).
- To date we have conducted more than 70 analyses within a time span of two and a half years. This analysis is limited to 30 programs/protocols that are posted on clinicaltrials.gov across five therapeutic areas.
- This study provides an understanding how of observational data can inform clinical trial design using the OHDSI framework and tools.

Methods

- The results of each of the analyses are summarized into a dataset which includes therapeutic area, key analysis questions, the number of criteria evaluated by domain (administrative, condition, drug, measurement, observation, and procedure), age distribution, individual results, match rates (the proportion of persons to match all criteria in the index cohort), data sources, and cohort size were recorded.
- Statistics were calculated by therapeutic area for various metrics, specifically: match rate, data domains of criteria, percentage of criteria evaluated/not evaluated which reflect the degree to which the criteria from the CT could be implemented in the observational data.

Results

- In total, 17% represent protocols recruiting from pediatric populations, while 7% were mixed adult and child and 76% adult.
- Table 1 gives the overall statistics of criteria by type and percent evaluated. Overall each protocol has on average 33.1 criteria with 55.59% of criteria that can evaluated through available observational data.

Table 1. Overall statistics of evaluated programs using the clinical trial feasibility framework

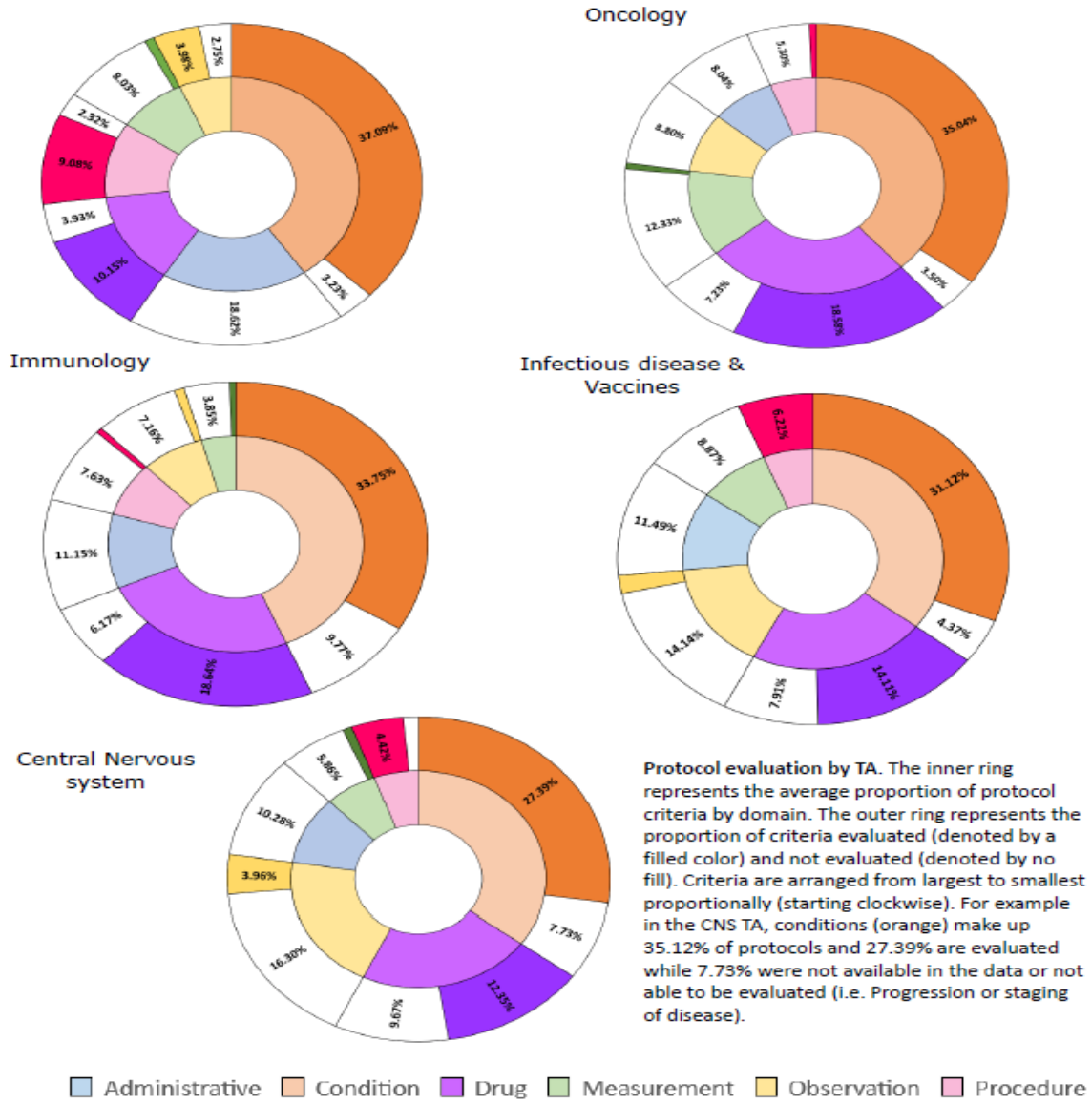
Therapeutic Area ǂ	N	Average number protocol criteria	Average number inclusion criteria	Average number exclusion criteria	Percent protocol criteria implemented
CNS	9	34.5	11.1	23.4	48.18%
CVM	4	29.0	9.0	20.0	59.89%
IDV	4	28.3	11.5	16.8	53.21%
IMM	7	51.0	16.8	34.1	57.23%
ONC	6	22.6	8.7	14.0	59.44%
Overall	**30**	**33.1**	**11.4**	**21.7**	**55.59%**

ǂ Therapeutic area: (CNS=Central Nervous System, CVM=Cardiovascular & Metabolism, IDV=Infectious disease & Vaccines, IMM=Immunology, ONC=Oncology)

Results

- The proportion of criteria in a protocol vary by domain with conditions making up over 30% of the protocol criteria across domains followed by drugs, procedures, observations, measurements and administrative criteria.
- In all TA's conditions make up the majority of criteria that is evaluated with at least 27% of condition criteria evaluated.
- Administrative data is not evaluated in any TA due to the lack of this data type, examples include: consent to participate or adherence to protocol guidelines. Measurement data which is mainly laboratory data is evaluated for less than 1% of criteria due to lack of completeness of data for all persons in the disease cohorts.
- The differences in the amount of criteria by domain represent comorbidities that are relevant to individual TA's, for example immunology and oncology have a larger proportion of drug criteria compared to cardiovascular protocols.

Figure 1. Protocol evaluation by therapeutic area

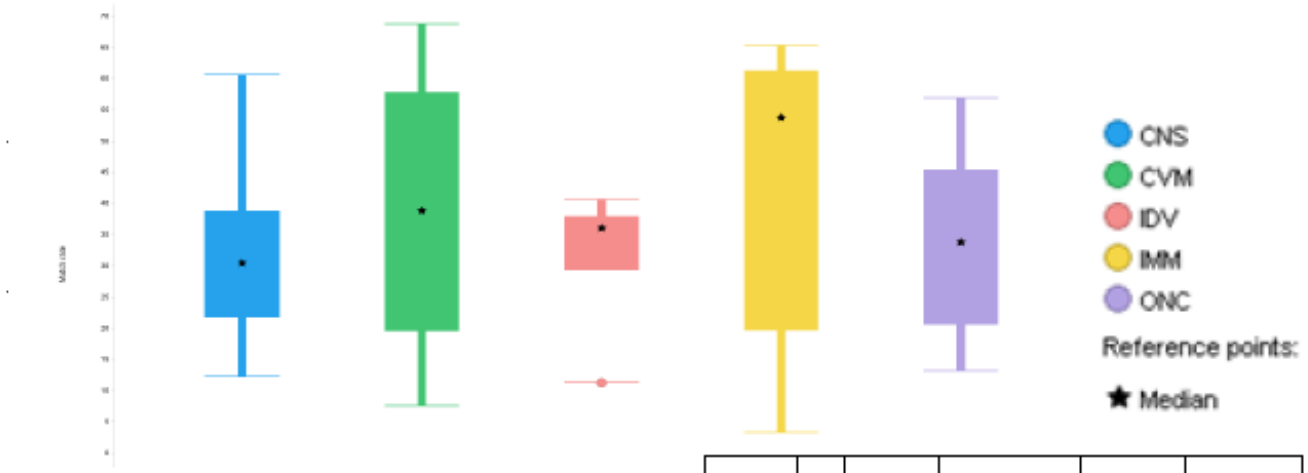


Protocol evaluation by TA. The inner ring represents the average proportion of protocol criteria by domain. The outer ring represents the proportion of criteria evaluated (denoted by a filled color) and not evaluated (denoted by no fill). Criteria are arranged from largest to smallest proportionally (starting clockwise). For example in the CNS TA, conditions (orange) make up 35.12% of protocols and 27.39% are evaluated while 7.73% were not available in the data or not able to be evaluated (i.e. Progression or staging of disease).

Results

- The match rates vary among the TA's and by protocol. The matching population can vary from ~3% to 70% depending on the index population and disease area.

Figure 2. Match rate by therapeutic area



Match rate by TA. Each boxplot represents the range of match rates from protocols within each TA. The median match rate is denoted by a star within each box plot. Key values from the boxplot are represented in the adjacent table.

TA ‡	N	Min	Median	Max	IQR
CNS	9	12.2	30.42	60.57	17.13
CVM	4	7.55	38.81	68.69	38.31
IDV	4	11.27	36.08	40.63	8.71
IMM	7	3.35	53.72	65.25	41.64
ONC	6	13.19	33.77	56.86	24.74

Conclusions

- Our study demonstrates the value of using the OHDSI tools to support generating real-world evidence that can meaningfully inform clinical trial design. The observed diversity in match rates and impact of criteria demonstrate the need for feasibility to gain additional insights.
- Clinical trial inclusion criteria can often, but not always, be evaluated in observational data. When these criteria can be evaluated, they are most often based on prior conditions and medication history of the patient.
- The impact of inclusion criteria on the proportion of patients from a target population that satisfy all criteria can be evaluated using OHDSI tools, and the substantial variability shown in this study demonstrates that different types of insights can be obtained in different circumstances.
- While the use of observational data should be tailored to the particular clinical problem and the needs of the decision-making stakeholders, we believe a consistent process for applying standardized analytics can be applied to trial feasibility to meaningfully inform clinical development.
- Future research would be to evaluate the results from published trials against our implementation to determine the generalizability using observational data.

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