Development of a dynamic Parkinson's Disease database with user interface tools as a basis for internal and regulatory decision making

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BACKGROUND

- Parkinson's Disease (PD) drug development faces challenges around heterogeneity in disease progression, lack of validated biomarkers, and impact of symptomatic PD medications that mask drug effects.
- The composite endpoint Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) has been used for efficacy studies, but both sponsors and regulators face challenges in the most optimal subset of the scale to define meaningful change in disease course
- The Critical Path for Parkinson's consortium is a public-private partnership that works to integrate data precompetitive to help facilitate solutions for PD endpoint design among, among other efforts.

OBJECTIVES

- The objective of this work is to integrate multiple PD clinical studies, harmonize the data, and deploy a user interface for rapid data interrogation and analysis subset generation.

METHODS

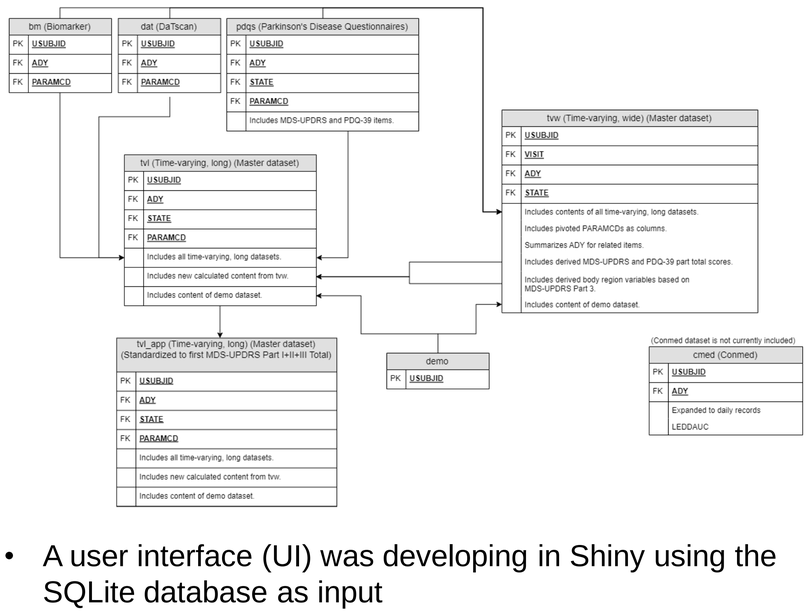
- Multiple PD clinical datasets were obtained from the Critical Path for Parkinson's Consortium (ref 1) and Biogen internal PD studies, including randomized clinical trials (RCTs) and observational PD studies
- Datasets were standardized to CDISC SDTM and integrated into analysis domains for demographic, biomarker, and endpoint data.
- A SQLite database was developed and used as the input into a web-based dynamic user interface (UI) developed using Shiny (R package for developing web applications) for data interrogation.
- The Shiny UI was developed to give versatile and simple to use tools for broad audiences within a clinical development team, with additional functionality for analysis subsets to be efficiently generated

RESULTS - DATABASE

- A total of 9 clinical studies (6 RCTs, 3 observational) were standardized and integrated into a SQLite database [see below]

Study	Contributor	Study Type	Reported Number subjects	Years since Dx	Duration of follow up
PPMI	MJFF	Obs	1866	de novo	Ongoing (2010)
Tracking PD	U of Glasgow	Obs	1998	de novo	3-5 years
STEADY-PD3	MJFF/U of Rochester	RCT	336	<3	3 year
SPARK	Biogen	RCT	357	<3	<2 year
BEAT-PD	Biogen	Obs	33	<5	3 years
SURE-PD3	MJFF/U of Rochester	RCT	298	<3	2 years
Azilect Ph3	Takeda	RCT	244	<5	0.5 years
Azilect Ph3 LTE	Takeda	RCT	171**	<5	1 year
PASEDENA Ph2	Roche	RCT	100	<2	1 year

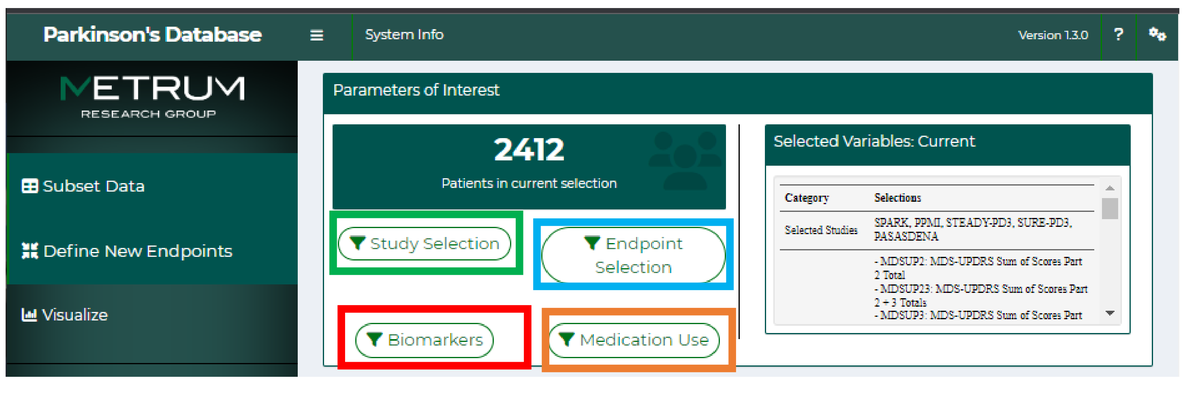
- Extensive data standardization based on CDISC STDM was used to generate intermediate analysis domains across the various data types including demographics, biomarkers, medication information, and clinical assessments [see below]

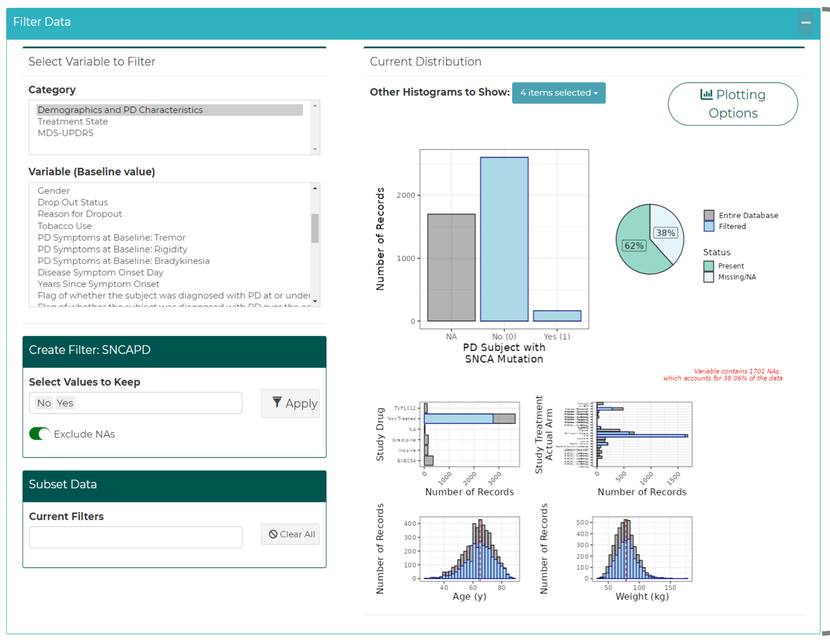


- A user interface (UI) was developing in Shiny using the SQLite database as input

RESULTS – USER INTERFACE

1) Key Data Selection: Define underlying population and associated measures by selecting from available **studies** (as singletons or combined subsets) as well as **clinical endpoints**, **biomarkers**, and time-varying **medication use**.



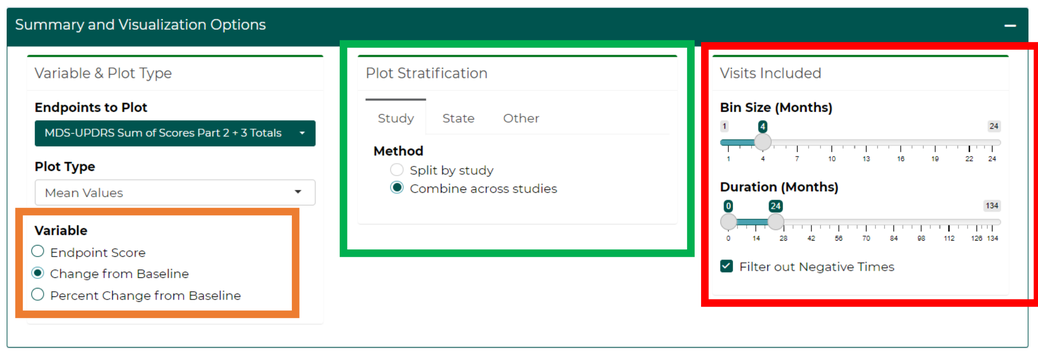


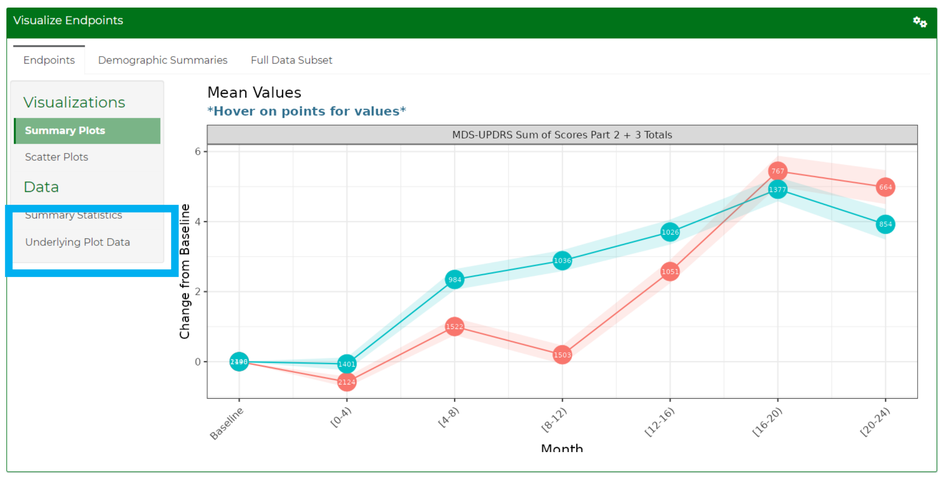
2) Baseline Feature Visualization: Visualize the distribution of all available baseline variables in databased defined by key data selection. Users have the option to filter by variables and interest and save filters to examine various subpopulations. Missing data is clearly reported to give accurate representations of data completeness.

Defined subpopulations can be saved and loaded for future use. The filter criteria are also recorded to help track and compare different subpopulations.

3) Define Customized Endpoints: Users can define custom endpoints by selecting individual items from composite measures, or entire composites, and sum them. Items from individual parts MDS-UPDRS

4) Visualize Endpoint Trajectories: Longitudinal trajectories can be visualized with options to **choose duration and binned time intervals** and **stratify by continuous & categorical variables**. For continuous variables, users can choose custom thresholds to divide the underlying population.

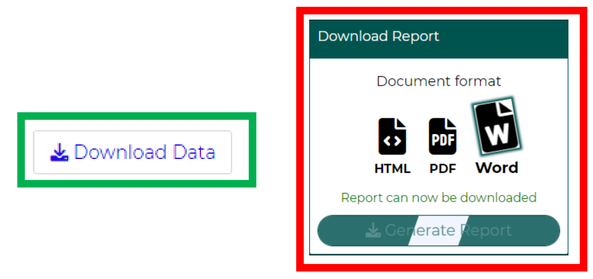




Extensive plotting options enable users to customize figure views and real time values for easier interpretation. **Endpoints** can be shows as raw values, change from baseline, and percent change from baseline

User can generate **summary statistics** of the chosen population and **view the raw data** as well.

5) Downloadable raw data: Users can **download raw data** in Analysis Data Model (ADaM)-like structure. This features helps minimize additional data processing for software input. The data structure is amenable for use in NONMEM, Monolix, and Stan. Additionally, users can **download a report** that collects are data filter criteria, generated tables, and figures including baseline and longitudinal plots into a single report. Output options include HTML, PDF, and Word, with figures and tables embedded as standalone for eacy retrieval.



CONCLUSION

The developed PD dynamic database and user interface tools offers several advantages for analyzing clinical data:

- **Accessibility** – The UI allows for audiences of diverse background to interrogate the data without the need for explicit coding
- **Efficiency –** Real-time filtering and visualization of the data is automated, requiring little time for data analysis
- **Scalability –** New data (likely in SDTM already) can be readily integrated into the database using the existing database structure
- **Open source –** UI and underlying data structure are developed with well known, open-source tools making them easily sharable

#The authors recognize the Critical Path for Parkinson's consortium of the Critical Path Institute for generously sharing of the patient and item level data from the CPP Parkinson's Integrated database to support the analysis presented here.