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White Paper:

U.S. Food and Drug Administration (FDA) Inventory of Clinical Trials Protocols and Clinical Study Data

August 31, 2011

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Acknowledgements: This study was conducted under contract HHSF223201011356P and was co-funded by the Food and Drug Administration and the Assistant Secretary for Planning and Evaluation Office of Science and Data Policy, Department of Health and Human Services.

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Glossary of Project-Specific Terms

To distinguish usage throughout the text:

- *Italics* indicate a study, project, or database term
- ”Double quotation marks” indicate first or unique usage of a specific term
- Initial Capital Letters (for what is otherwise a generic term) indicate a database table or field name

The glossary below defines project-specific terms.

Term	Definition
Chronic Condition	Study chronic conditions were identified by the Technical Advisory Group (TAG) as being of interest in the study. Chronic conditions are prolonged in duration, do not resolve spontaneously, and are rarely cured completely
Chronic Conditions for Exclusions	Study exclusion criteria were defined by the project TAG as being of interest for analysis. Because study data were found to contain a condition not present in the medical histories, an additional SNOMED term, *at risk for injury*, was added for possible study exclusion. This term reflects the broad statement found in many protocols that excludes subjects for whom, in the opinion of the investigator, participation in the clinical trial would be detrimental to their health.
Chronic Conditions for Medical History	Based on subjects’ medical history, nineteen (19) chronic condition categories were defined by the project TAG as being of interest for analysis.
Condition Treated	This term refers to study indication—a primary condition that the clinical trial is assessing.
Data Definition	This term is used in the FDA filing system to describe the data structure of the submitted data.
Data Elements	This term includes four types of data: (1) study characteristics, (2) study-level exclusion criteria, (3) subject-level demographic data, and (4) subject-level medical history data.
ICD-9-CM	The International Classification of Diseases, Ninth Revision, Clinical Modification is based on the World Health Organization's classification of diseases.
Project Standard Structure	This term represents the data structure developed for the project database.
TAG	The Technical Advisory Group members included FDA and HHS staff assigned to the project.

U.S. Food and Drug Administration (FDA)

FDA Inventory of Clinical Trials Protocols and Clinical Study Data

1 Executive Summary

1.1 Background

Though the FDA has regulatory tracking systems such as the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), the agency does not have a scientific reference database to query clinical trials by trial design elements and other key parameters. Digital Infuzion collaborated with FDA to design, develop, and implement a scientific reference database with the capabilities to standardize unstructured electronic formats based on Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (STDM) standards and to query clinical studies by trial design and keywords.

The primary question to be addressed was whether individuals with multiple chronic conditions (MCCs) are being excluded from controlled clinical trials. The scope of the project included New Drug Applications (NDAs) and Biologic License Applications (BLAs) submitted with electronic data during fiscal year 2010. One hundred and forty-seven studies met the criteria for inclusion in this analysis.

1.2 Key Findings

Five areas for evaluation were defined with the project Technical Advisory Group (TAG):

1. Study characteristics
2. Study population characteristics
3. Whether patients with chronic conditions are being excluded from trials
4. Extent to which chronic conditions are included or excluded by indication
5. Co-occurrence of chronic conditions

FDA data sources, together with ClinicalTrials.gov, were utilized to populate the new dataset. ClinicalTrials.gov proved to be only a peripheral data source for the project, since it often contained information that was discrepant with completed study information submitted to FDA.

The current database population of clinical trials data was created from 42 different *conditions treated* across 147 studies and 115,342 subjects. Published information on the general population was explored to determine if the clinical trials data were reflective of general population statistics. ”Screening logs” containing information on individuals who had been evaluated for clinical trials participation, but possibly rejected because of co-occurring chronic conditions, are not submitted to FDA, precluding a direct comparison of the subjects enrolled versus excluded subjects. The available data provide an evaluation of chronic conditions for the enrolled subjects, without information as to those excluded. In addition, the appropriateness of subject exclusion should give consideration to factors such as the demographics of the population being studied, stage of condition being treated, the treatment mode of action, and profile of metabolic interactions with other medications.

Despite these limitations, database trends relating to the distribution, occurrence, type, and count of chronic conditions paralleled the available published statistics, permitting some conclusions about the clinical trials population and MCCs. Certain exclusion criteria appear to be more closely adhered to than others, based on the percent of subjects who were enrolled into clinical trials with MCCs. Also, in the clinical studies examined, the prevalence of several chronic conditions was lower than that reported in the general population. Additional evidence suggesting that some subjects with MCCs are excluded from clinical trials appeared in studies focused on hypertensive disease and hyperlipidemia, where the coexistence of conditions considered to be clinically associated with these diseases was less than the occurrence in the overall database population.

2 Introduction

The number of co-occurring MCCs is increasing in an aging population. The number of Americans with MCCs is projected to be 81 million by 2020.[1] As indicated in Table 1, among individuals age 18–64, 45% have one or more and 20% have two or more chronic conditions.[2] Ninety-one percent of those age 65+ have one or more and 73% have two or more chronic conditions.[3]

Table 1. Percent of Americans with Co-Occurring MCCs by Age Group

	Percent of Americans with MCCs	
Age Group	1 or more Chronic Conditions	2 or more Chronic Conditions
18 – 64	45%	20%
65+	91%	73%

Women have a higher prevalence of chronic conditions across the entire population. The aging U.S. population and growing number of individuals with MCCs require that clinical treatment guidelines consider not only the primary disease being treated, but also the finding that an accompanying comorbidity can exert an additional negative impact on the condition being studied. For example, the effect of depression on a comorbid condition has been extensively reviewed; it was found that depression adversely affects a patient's adherence to the medication and treatment plan for other comorbid conditions. The Office of the Assistant Secretary for Health has expressed concern that efforts targeted at treating individual diseases have inadvertently limited the knowledge of how to effectively treat subjects with MCCs.[4]

[1] Anderson G, Horvath J. The growing burden of chronic disease in America. Public Health Reports 2004; May-June:263–270.

[2] Anderson, 265.

[3] Robert Wood Johnson Foundation, Published February 2010, Accessed August 2011, www.rwjf.org/pr/product.jsp?id=50968

[4] Parekh AK, Barton MB. The challenge of multiple comorbidity for the US health care system. JAMA 2010; 303(13):1303–1304.

The U.S. healthcare system utilizes a significant amount of prescription medications to treat patients with chronic conditions. Such patients are likely to be taking multiple medications for different conditions, often prescribed by different providers. People with five or more chronic conditions fill almost 50 prescriptions per year.[5] The management and interactions of multiple medications is not only a challenge to providers, but also to patients who try to participate in their own care. If patients with MCCs are excluded from clinical trials, nothing can be learned about the effect of treatments on those conditions or about possible interaction of those conditions with the test treatment.

The most prevalent individual conditions documented among the Medicare population are arthritis (57%), hypertension (55%), pulmonary disease (38%), diabetes (17%), cancer (17%), and osteoporosis (16%).[6] Within the Medicare population, more information on MCCs has been evaluated and made public. A large study of Medicare claims was conducted using ICD-9-CM and claims data for 2008.[7] The study focused on Medicare expenditures and found that multiple, complex disease combinations were the primary drivers of health care utilization and costs. For this FDA project, electronic data submitted to FDA on NDAs and BLAs for 2010 were utilized to evaluate the presence of chronic conditions for subjects enrolled in clinical trials. The obvious next step would be to compare the incidence of chronic conditions in the pooled clinical trials examined in this report with the incidence of chronic conditions observed in other settings. Unfortunately, published data on the prevalence of various comorbidity clusters in the general population are either limited or not comparable to the patient population pooled examined in this report due to the use of different methodologies for creating chronic condition groups. Nonetheless, to assess the potential exclusion of individuals with MCCs in controlled clinical trials, comparisons of prevalence and disease trends were made between the clinical trials subjects and general population wherever published data were available.

3 Project Scope and Methodology

3.1 Scope of Project

The FDA does not have a scientific reference database that allows systematic searches of clinical studies for trial design elements and other key parameters. Many trials exist in unstructured electronic formats, and the content is only known to domain experts with relevant historical experience.

The goal of the current project was to develop a database and access tool to determine if:

1. Individuals with MCCs are being excluded from controlled clinical trials, either by entry criteria or in practice
2. Exclusions differ by condition treated

[5] Benjamin, RM. Multiple chronic conditions: A public health challenge. Public Health Reports 2010; September-October; 125:626-627.

[6] Vogeli C, Shields AE, Lee TA, Gibson TB, Marder WD, Weiss KB, Blumenthal D. Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. J Gen Intern Med 2007; 22(suppl 3):391–395.

[7] Sorace J, Wong H-H, Worral C, Kelman J, Saneinejad S, MaCurdy T. The complexity of disease combinations in the Medicare population. Population Health Management 2011; 14:1-6.

3. MCCs research questions can be addressed by pooling subject-level data
4. There are limitations of current clinical trial data format, storage, and location that interfere with answering the above

3.2 Parameters

3.2.1 Study selection

3.2.1.1 Pilot phase

Ten NDAs / BLAs from fiscal year 2010 submissions were identified by the FDA for data collection in the Pilot phase of the project. Only Phase 3 protocols (”studies”) in these ten applications were retrieved as part of the pilot, yielding approximately 40 studies in the Pilot phase. Upon review of the subject medical history terms from the pilot studies, the TAG developed the 19 chronic condition groupings discussed in Section 4.2.2.

3.2.1.2 Production phase

The remaining NDAs / BLAs from the list of FY2010 submissions provided by the TAG were collected for the Production phase of the project, based on the selection parameters established in the Pilot phase (studies with submitted electronic subject-level medical history data, not including extension studies). In addition, the selection scope was expanded to all Phase 3 and Phase 4 studies, as well as Phase 2 oncology studies.

3.2.2 Identification of chronic conditions

A list of terms that were clinically considered to represent *chronic conditions* was prepared during the Pilot phase. Next, tabulations of the individual subject medical history and study exclusion criteria were searched for *chronic condition* terms. This list was parsed into terms that fell within the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) dictionary of Fully Specified Name (FSN) terms. The list was reviewed by the project TAG and generally consolidated utilizing the SNOMED CT hierarchy into a final list of chronic conditions of interest. Some SNOMED terms were moved to different groupings, reflecting clinical interpretation. All verbatim terms were retained in the database to allow future coding variations.

An additional SNOMED term, *at risk for injury*, was added to reflect the broad statement found in many protocols that excludes subjects for whom participation in the clinical trial would be detrimental to their health, in the opinion of the investigator. This subjective evaluation allows for the possible exclusion of subjects at the discretion of the investigator.

The list of chronic conditions is presented below, and the associated FSN terms in each category are in Appendix 1.

Arthritis and Arthropathy

At Risk for Injury (only relevant for Exclusion Criteria)

Atherosclerotic Cardiovascular Disease

Autoimmune Disorder

Chronic Infectious Disorder

Diabetes Mellitus

Dyslipidemia

Endocrine / metabolic Disorder

Gastrointestinal Disorder

Genitourinary Disorder

Heart Disorder

Hepatic Disorder

Hypertensive Disease

Kidney Disorder

Multisystem Disorder

Neoplasm

Neurological Disorder

Psychiatric Disorder

Pulmonary Disorder

Vascular Disorder

3.2.3 Data coding

After consultation with the FDA TAG, SNOMED CT was deployed in this project as the coding terminology for MCCs. SNOMED CT is an extensive clinical terminology that was formed by the merger, expansion, and restructuring of SNOMED Reference Terminology (SNOMED RT(r)) and the United Kingdom National Health Service Clinical Terms (also known as the Read Codes). SNOMED CT is concept-oriented and has an advanced structure that meets most accepted criteria for a well-formed, machine-readable terminology. It has been designated as a U.S. standard for electronic health information exchange in Interoperability Specifications produced by the Healthcare Information Technology Standards Panel. SNOMED also has been adopted and mandated by the U.S. Federal Government, through the Consolidated Health Informatics Initiative, for several clinical domains, after being recommended by the National Committee on Vital and Health Statistics.

4 Data Collection

4.1 Identification of Project Data Elements and Corresponding Data Sources

The core data elements were identified based on specifications in the project statement of work (SOW). A data element inventory was developed, supplemented by corresponding data fields found in ClinicalTrials.gov. The inventory was used as a template to identify the corresponding data sources in the FDA NDA / BLA submissions systems. The Pilot phase studies were used to determine appropriate study-level and subject-level data sources.

The core data elements include four types of data: (1) study characteristics, (2) study-level exclusion criteria, (3) subject-level demographic data, and (4) subject-level medical history data.

4.2 Establishment of Data Standards for Study-Level and Subject-Level Data

Data standards for the study characteristics were based on the Clinical Study Report (CSR) and certain downloadable fields in ClinicalTrials.gov. Data standards for the exclusion, demography, and medical history data were based on corresponding domains of Trial Inclusion/Exclusion Criteria (TI), Demographics (DM), and Medical History (MH) in CDISC-SDTM.

4.3 Development of Database and Data Handling Procedures

4.3.1 Database development

In collaboration with the TAG, the project team defined four core data tables to meet SOW objectives:

1. The Study-Level table describes the condition treated in each study. It contains study characteristics data found in the CSR and other clinical trials documentation submitted to the FDA. Database fields were created for each item in the SOW specifications, to correspond with fields in ClinicalTrials.gov and in the clinical trials documentation submitted in the FDA. The table structure includes fields to accommodate the medical coding of the Condition Treated and tracking-data fields to facilitate the data collection process.
2. The Exclusion table describes the specific conditions excluded in each study. It contains the study-level exclusion criteria specified in the CSR for each study. The table structure includes selected fields from the SDTM TI domain, along with additional fields to accommodate the medical coding of chronic conditions described in the exclusion criteria.
3. The Demography table contains the subject-level demographic data in the electronic datasets submitted to the FDA for each study. The table structure includes selected fields from the SDTM DM domain and an additional field to accommodate standardization of the study drug assignment data.
4. The Medical History table contains the subject-level medical history data in the electronic datasets submitted to the FDA for each study and allows identification of the concomitant illnesses, particularly chronic illnesses, that each patient had in addition to the condition being treated. The table structure includes selected fields from the SDTM MH domain and additional fields to accommodate the medical coding of chronic conditions.

The final data elements were created in a master database. Utilizing applicable standard formatting established in SDTM and ClinicalTrials.gov, tables and fields (collectively referred to as “data elements”) were documented along with their formatting and standard code lists. The data elements specifications were reviewed and approved by the TAG.

4.3.2 Database handling procedures

4.3.2.1 Data capture

Study-level and subject-level data were captured in a spreadsheet file format prior to processing into the master database.

Study-level data were extracted from the CSR and other clinical trial documentation in the FDA NDA / BLA submission systems and entered into the data inventory template.

Study-level Exclusion data were retrieved in one of two ways: (1) For studies that submitted electronic SDTM-formatted data files, the data were retrieved as a spreadsheet file and standardized to the approved data elements specification. (2) For studies where electronic data files were not submitted, the exclusion information was retrieved from the CSR, extracted and standardized to the approved data elements.

For subject-level Demography and Medical History data, the appropriate data files were identified in the FDA NDA / BLA submission systems and processed into the master database. These raw data files were standardized to the approved data elements. Any subjects in the Demography or Medical History data who were identified as screen failures were removed from the standardized dataset. Also, any duplicate or extraneous records in the Medical History data were removed. To ensure proper transfer of the data to the master database, the original study data definition was mapped to the project standard structure. Retrieval of the dataset was tracked in the Data Inventory table and captured in the Study Level table.

So that dataset size would be optimal for import and data processing activities could continue in parallel to data retrieval, datasets were processed by batches of approximately 30–35 studies each.

4.3.2.2 Data coding

After standardization into SDTM domains, CliniClue Xplore (developed by Clinical Information Consultancy, Ltd.) was used to machine code study-level exclusion criteria and subject-level medical history data into a standardized terminology. To preserve the confidentiality of patient-level data, a table of unique medical history terms was generated from the master database. This table of unique terms was put through the coding process described below.

The list of unique terms were manually reviewed and parsed into standardized terms that could be read by the medical coding tool. Terms were reviewed to determine if they corresponded to a *chronic condition of interest*. Terms that did not qualify for coding were manually reviewed, then flagged so that the medical coding tool would omit those terms from any further coding activity. Terms that did qualify for coding were assigned a standardized term for each criteria condition. The standardized terms to be coded were then processed through the medical coding tool; the coded data were reviewed to ensure that all terms coded as expected. Where standardized terms did not code because of a remediable reason (due to inconsistency in spelling, for example), the terms were revised to obtain the proper match in the SNOMED CT dictionary and put through the coding process again.

The above process was continued until all medical history terms in the unique-term table were properly coded or omitted. After the unique-term table coding was finalized, the table was merged back into the original Medical History table by matching the original terms between the two tables. The coded data populated to all original subject-level medical history terms.

4.4 Data Validation Process

4.4.1 Study-level data

Following data retrieval for each batch, Study Level Data Inventory data fields and Exclusion Criteria were verified against their original source in the FDA NDA / BLA submission systems to ensure that the data captured matched the source.

After import to the master database was completed, the dataset for all 147 studies was verified against the original source in the FDA NDA / BLA submission systems. Further, to ensure there were no discrepancies between the study identifiers in the key and the imported file, the imported Study IDs were verified against the Study Key.

5 Findings

In reviewing the findings presented in this section, bear in mind that clinical trials subjects must have the *condition treated* (condition being studied for a specific protocol) in order to be enrolled, and many of the conditions being studied are themselves chronic conditions. Since the principal interest in this effort was to determine whether people with chronic conditions other than the condition under study were being excluded from trials, the findings presented here would be biased towards the type and number of studies in the database if the chronic condition required for study enrollment was counted as a chronic condition in the subject's medical history. Therefore, if subjects had a chronic condition in their medical history that was the same as the study *condition treated*, the term was not counted.

5.1 Study Characteristics and Exclusions

The MCCs project database contains 147 studies from 52 NDAs / BLAs submitted to FDA in FY2010. Actual study start dates ranged from July 17, 1998, to September 2, 2009. The study start date was defined as the date upon which the first subject was enrolled. The average length of the studies was 18 months, with a range from 1 to 75 months. Most studies (87%) were between 7 and 30 months duration.

There were 42 different *conditions treated* across the 147 studies. The five most frequent *conditions treated* were *hypertensive disorder*, *diabetes mellitus*, *malignant neoplastic disease*, *obesity*, and *psoriasis* (42% of studies). A complete list of the *conditions treated* and their frequency is found in Appendix 2.

Three types of endpoints were defined for characterizing the studies (Table 2). *Signs*, defined as an objective indication of some medical fact or characteristic detected by a healthcare professional (e.g., blood pressure or weight), represented the predominant endpoint at 88.4%. Signs included outcome measures such as those found in oncology studies, e.g., time to disease progression or disease free survival, as well as established symptom scores used in depression, arthritis, and many pulmonary disease trials.

Table 2. Endpoints for Characterizing Studies

Endpoint Type	Number of Studies (%)
Signs	130 (88.4%)
Symptoms	9 (6.1%)
Laboratory Values	8 (5.4%)

The average number of exclusion criteria per study was 7.9 (range 0–16). Categorization of exclusion criteria, utilizing SNOMED CT, produced the same groups as the project-defined *chronic conditions*, with the one addition *at risk for injury*. *At risk for injury* is only relevant to protocol exclusions and captures the broad statement found in many protocols that excludes subjects for whom, in the opinion of the investigator, study participation would be detrimental to their health.

Table 3 presents the list of study exclusion terms (chronic condition groups from coded exclusion criteria) and the number of studies that contained each term. The number of studies containing each exclusion group is presented for all 147 studies (center column). In the right column, studies were the exclusion was the same as the *condition treated* were removed from the analysis. For example, hepatic disorder was an exclusion group found in 114 of 147 studies, but for 2 studies the *condition treated* was hepatic disorder so when these are excluded from the analysis, the criterion leaves 112 studies. Seven exclusions are found in over half of the protocols, as demarcated in Table 3.

Table 3. Study Exclusion Terms and Number of Studies that Contained Each Term

Study Exclusion Groups	Number of Studies (%)	Number of Studies (%) Excludes Trials Studying the Condition Treated
Hepatic Disorder	114 (77.6%)	112 (76.2%)
Psychiatric Disorder	113 (76.9%)	104 (70.8%)
At Risk For Injury	108 (73.5%)	108 (73.5%)
Neoplasm	100 (68.0%)	87 (59.2%)
Heart Disorder	97 (66.0%)	97 (66.0%)
Kidney Disorder	92 (62.6%)	92 (62.6%)
Atherosclerotic Cardiovascular Disease	81 (55.1%)	81 (55.1%)
Diabetes Mellitus	69 (46.9%)	56 (38.1%)
Neurological Disorder	63 (42.9%)	55 (37.4%)
Chronic Infectious Disorder	52 (35.4%)	49 (33.3%)
Hypertensive Disease	52 (35.4%)	32 (21.8%)
Pulmonary Disorder	49 (33.3%)	49 (33.3%)
Endocrine/Metabolic Disorder	47 (32.0%)	35 (23.8%)
Gastrointestinal Disorder	42 (28.6%)	35 (23.8%)
Vascular Disorder	25 (17.0%)	25 (17.0%)
Autoimmune Disorder	24 (16.3%)	16 (10.9%)
Multisystem Disorder	11 (7.5%)	11 (7.5%)
Arthritis and Arthropathy	9 (6.1%)	3 (2.0%)
Dyslipidemia	5 (3.4%)	4 (2.7%)
Genitourinary Disorder	1 (0.7%)	1 (0.7%)

*One study had no exclusion criteria.

In the database population, the most common chronic condition exclusions were *hepatic disorder*, *psychiatric disorder*, and *at risk for injury* (77.6%, 76.9%, and 73.5%, respectively). These remained the top 3 most common chronic condition exclusions even when trials for each of these 3 conditions were not counted. *Hepatic disorder* and *at risk for injury* may be expected as frequent exclusion criteria because of their implications for subject safety. *Psychiatric disorder* exclusion is made up of the following list of study terms:

Adjustment Disorder

Agoraphobia

Alcohol Abuse

Anorexia Nervosa

Anxiety Disorder

Attention Deficit Hyperactivity Disorder

Bipolar Disorder

Bulimia Nervosa

Depressive Disorder

Drug Abuse

Drug-Induced Tardive Dystonia

Eating Disorder

Generalized Anxiety Disorder

Mental Disorder

Mixed Anxiety and Depressive Disorder

Obsessive-Compulsive Disorder

Posttraumatic Stress Disorder

Psychotic Disorder

Schizoaffective Disorder

Schizophrenia

Substance Abuse

The appropriateness of excluding subjects with psychiatric disorders from three-fourths of non psychiatric studies may be a subject for future study-specific review. The least frequent exclusions were for *genitourinary disorder*, *dyslipidemia*, then *arthritis and arthropathy*. *Hypertensive disease* was excluded in only about one-fourth of studies for non-antihypertensive indications.

The *conditions treated* that contained the most exclusions were *low back pain* (14.5), *viral hepatitis* (14), *hyperlipidemia* (13), and *neuropathy – diabetic* (12). Those with the least number of exclusions included *cystinosis* (0), *contraception* (1), *Gaucher disease* (2), *cystic fibrosis* (2.5) and *acute coronary syndrome* (3). The complete list is presented in Table 4.

Table 4. Conditions Treated and Corresponding Exclusions

Condition Treated	Number of Studies	Number of Exclusions (Mean)
Low Back Pain	2	14.5
Viral Hepatitis	2	14.0
Hyperlipidemia	1	13.0
Neuropathy – Diabetic	1	12.0
Sexual Dysfunction	5	12.0
Gastroesophageal Reflux Disease	4	11.0
Growth Hormone Deficiency	1	11.0

Condition Treated	Number of Studies	Number of Exclusions (Mean)
Osteoarthritis	5	11.0
Systemic Lupus Erythematous	2	11.0
Idiopathic Pulmonary Fibrosis	2	10.5
Gastrointestinal Ulcer	2	10.0
Depressive Disorder	3	9.3
Obesity	9	9.2
Hypertensive Disorder	20	9.1
Psoriasis	6	8.7
Multiple Sclerosis	2	8.5
Bipolar Disorder	1	8.0
Hypogonadism	1	8.0
Schizophrenia	4	8.0
ALL COND TREATED	147	7.9
Diabetes Mellitus	14	7.7
Postoperative Pain	3	7.7
Renal Transplantation	4	7.3
Infertility	1	7.0
Malignant Neoplastic Disease	13	6.7
Neuropathy – Postherpetic	2	6.5
Seizure Disorder	3	6.3
Attention Deficit Hyperactivity Disorder	1	6.0
Fibromyositis	2	6.0
Gout	2	6.0
Human Immunodeficiency Virus	4	6.0
Pneumonia, Bacterial	2	6.0
Genital Warts	2	5.0
Infection – Skin	2	5.0
Pancreatic Insufficiency	1	5.0
Inflammatory Disorder of the Eye	5	3.8
Diagnostic Imaging – CNS	3	3.7
Neutropenia – Chemotherapy Induced	3	3.3
Acute Coronary Syndrome	1	3.0
Cystic Fibrosis	2	2.5
Gaucher Disease	1	2.0
Contraception	2	1.0
Cystinosis	1	0.0

The presence of a chronic condition exclusion criterion in the same group as the study *condition treated* results from limitations that arise from a coding process that categorizes medical terms into groups. The result is a loss of detail for similar but not identical terms. For example, studies that treat diabetes mellitus have exclusion criteria that include the following terms: "uncontrolled diabetes", "unstable diabetes", "new onset diabetes", and "treatment with insulin within the last 3 months." In the process of coding the terms to the SNOMED FSN level and then to the next higher level of "disorder," all of these terms become part of the diabetes mellitus exclusion group. The database preserved the original, verbatim term and the FSN, so future research can be done with different levels of coding or other dictionaries.

5.2 Study Population Characteristics

A total of 115,342 subjects were included in the 147 studies (range 9 – 18,626; mean 785; median 505). The gender allocation was 54.3% female and 45.7% male. The majority of subjects were Whites (78.3%), with Blacks (9.8%) and Others (11.9%) accounting for the remaining subjects. Table 5 provides a distribution of the age groups. Those 65+ years of age represent 19% of the MCCs project database (the corresponding figure for the US population is 14%).

Table 5. Distribution of Study Population by Age Band

Age Band	Count	Percent
0–18	1,188	1
19–30	12,895	11
31–40	16,881	15
41–50	23,913	21
51–64	37,825	33
65+	21,961	19

*There were 679 subjects for whom Age was not reported; these subjects were not included in the Age Bands

The average number of chronic conditions is reported to increase with age. The current findings are consistent with this trend. Table 6 provides the average number of chronic conditions by age band. The average number of chronic conditions per subject is 1.8, increasing to 2.7 in the age 65+ group. As previously stated, if the subject had a chronic condition in their medical history that was the same as the study *condition treated*, the term was not counted.

Table 6. Distribution of Chronic Conditions by Age Band

Age Band	Average Number of Chronic Conditions
ALL	1.8
0–18	0.4
19–30	0.6
31–40	1.0
41–50	1.5
51–64	2.2
65+	2.7

Specific chronic conditions occurring most frequently within the age bands are listed in 7.

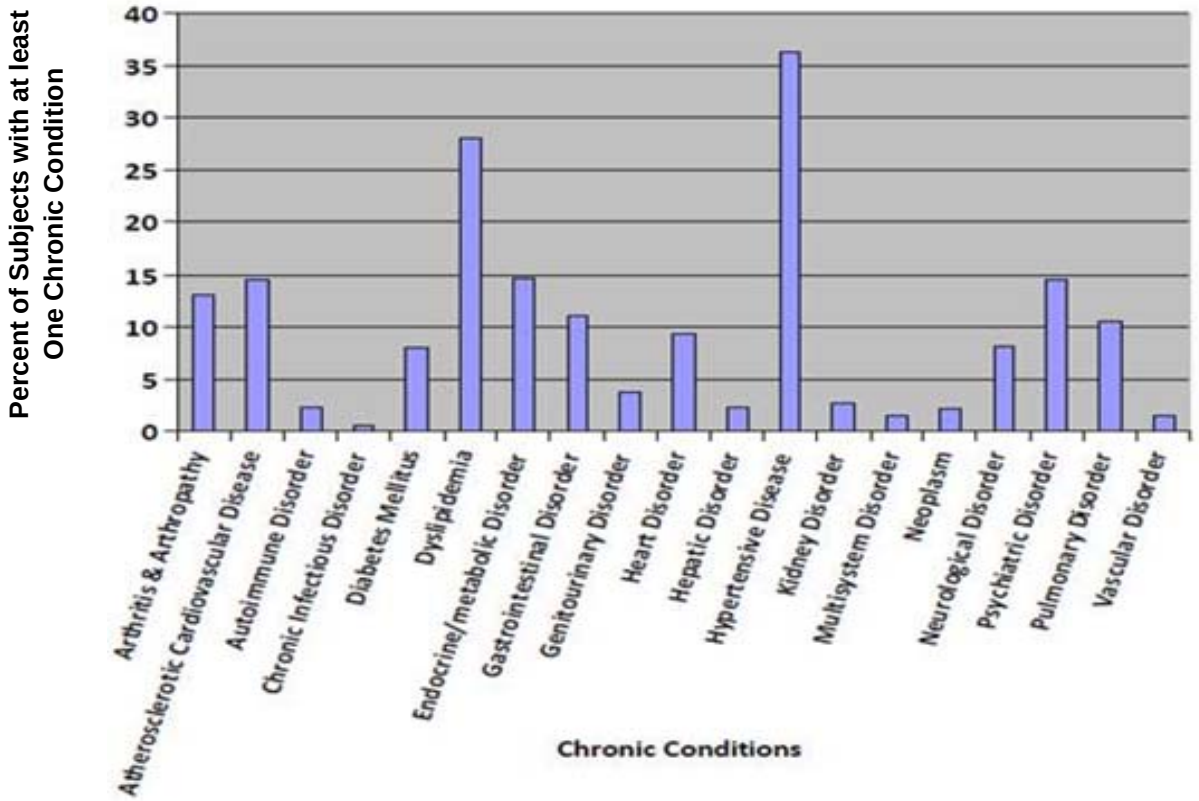
Table 7. Chronic Conditions Occurring Most Frequently by Age Bands

Ages	Chronic Conditions from Medical History
0–18	Pulmonary Disorder (9.9%), Neurological Disorder (5.6%)
19–30	Psychiatric Disorder (12.5%), Neurological Disorder (7.7%)
31–40	Psychiatric Disorder (14.9%), Dyslipidemia (11.3%)
41–65+	Hypertensive Disease (24.6–56.5%), Dyslipidemia (23.9%–42.5%)

Asthma has been cited as the primary chronic condition of childhood, and this agrees with the finding of pulmonary disorder as the most frequent chronic condition in the 0–18 age group.

The percent of all subjects with each chronic condition in their medical history is presented in Figure 1. To determine if these subjects were disproportionately represented in the relevant studies compared to the total population, the frequency was calculated based on both the total number of subjects for those studies in which they presented and the total database population. No large differences were found. Figure 1 shows that hypertensive disease and dyslipidemia were the most common chronic conditions in subjects' medical history records (36% and 28%, respectively). Some form of hypertensive disease was an exclusion criterion in 35% of studies and dyslipidemia in only 3%. Psychiatric disorder, endocrine/metabolic disorder, and atherosclerotic cardiovascular disease were each present in about 15% of the subjects' histories. The frequency of chronic conditions is influenced by the type of studies in the current database. Clinical trials for NDAs/BLAs submitted to FDA in FY2010 were the only studies examined. The types of chronic conditions and their frequency may change if there are more or fewer clinical trials focused on disease of an older population versus healthier young adults.

Figure 1. Percent Prevalence of Chronic Conditions in 147 Studies Submitted in FY2010



The presence of more than one co-occurring chronic condition defines MCCs for individual subjects. This was evaluated for the study population by counting the number of chronic conditions in each subject's medical history. Figure 2 shows the relative proportion of MCCs by age group. Figure 3 shows the percentage of patients by number of chronic conditions by age group. Both figures show that the number of chronic conditions increases as age increases.

Figure 2. Distribution of Multiple Chronic Conditions by Age Group

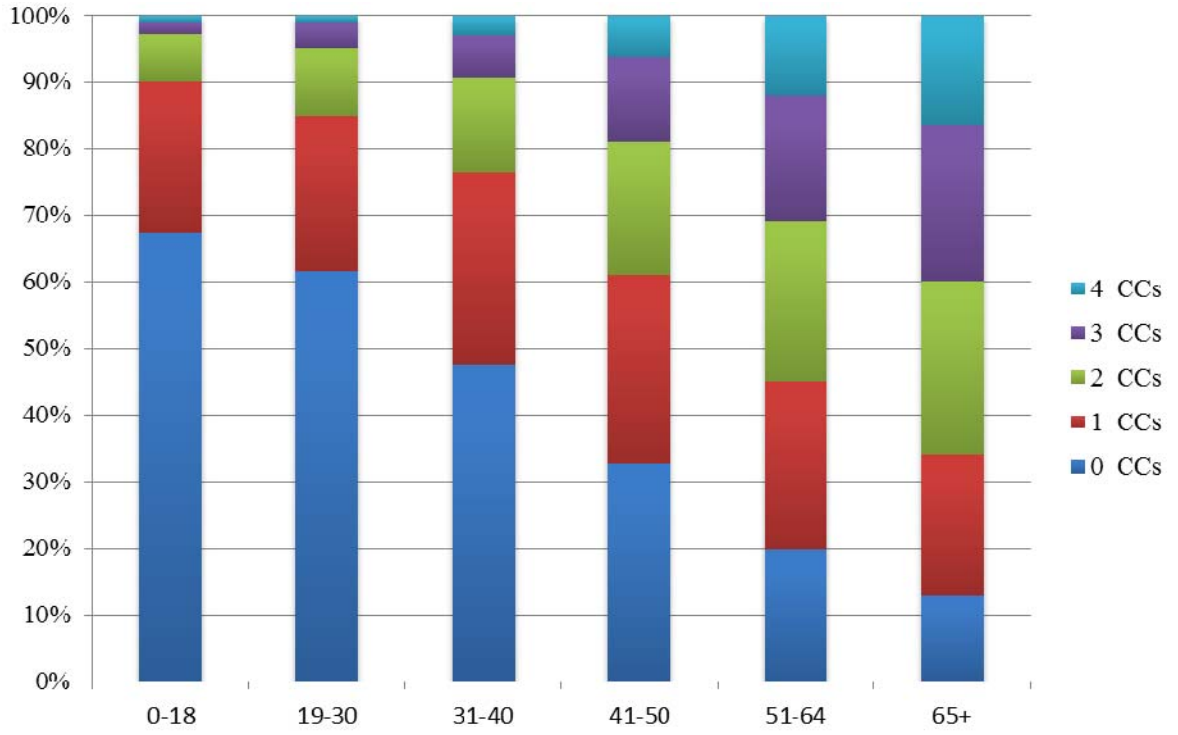
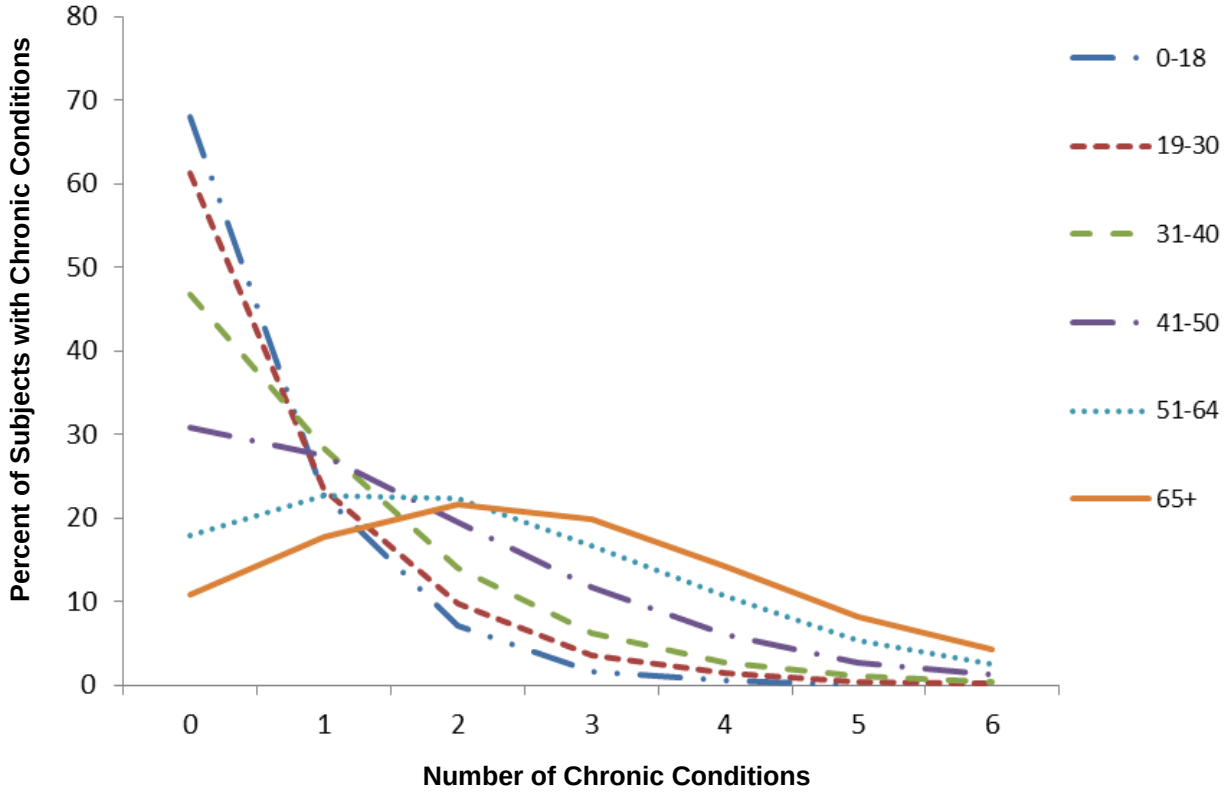


Figure 3. Change in Number of Multiple Chronic Conditions by Age Group



When available, published data were used as a benchmark to assess the presence or absence of subjects with MCCs in clinical trials, as reflected in Table . Within the 65+ age group, the presence of 1 or more chronic conditions has been reported at 90.7%, and 2 or more at 73.1%. This is comparable to the MCCs project database showing 89.2% and 71.5%, respectively

Table 8. Comparison of Database and Literature[8] Data for Multiple Chronic Conditions in the 65+ Age Group

Age 65+	≥ 1 Chronic Condition	≥ 2 Chronic Conditions
Database	89.2%	71.5%
Literature	90.7%	73.1%

In the database the number of chronic conditions was evaluated by sex and age (<65 years and ≥65 years). In the <65 group, females had a higher percentage with 1 or more chronic conditions than males; however, this trend reversed in the ≥65 group. Though females are reported to have a more complex medical profile in terms of the number and combination of chronic conditions, some specific chronic conditions occur equally or less often in females than males for both the <65 and ≥65 groups. These include atherosclerotic cardiac disease, diabetes mellitus, dyslipidemia, heart disorder, hepatic disorder, hypertensive disorder, and vascular disorder.

The clinical trials database cannot assess the profile of potential subjects who are screened but excluded due to MCCs. Comparisons can only be made to the publically available information that corresponds to the chronic condition groups that were established for this project. The published data focus primarily on the Medicare population for comparison. In several categories, the clinical trials data for MCC rates differ from the prevalence in the general population. Table 9 shows that the most striking differences are with respect to arthritis and arthropathy (57% in the literature versus 19% in the database), pulmonary disorder (38% versus 13%), psychiatric disorder (26% versus 11%), and malignant neoplasm (17% versus 5%). The latter is not surprising, as subjects with known malignant neoplasm would generally not be enrolled in clinical studies, unless malignant neoplasm was the *condition treated*.

[8] Robert Wood Johnson Foundation, 12

Table 9. Comparison of Chronic Condition Prevalence to Medicare Population Figures[9, 10]

Age 65+	Arthritis & Arthropathy	Diabetes Mellitus	Endocrine / Metabolic	Malignant Neoplasm	Pulmonary Disorder	Hypertension	Psychiatric Disorder
Database	19%	11%	19%	5%	13%	57%	11%
Literature	57%	17%	16%	17%	38%	55%	26%

One reason for the absence of subjects with MCCs enrolling in a clinical trial is the presence of explicit exclusion criteria. If this is a primary reason, one would expect a correlation between the number of exclusion criteria and the number of chronic conditions subjects have. The average number of chronic conditions per subject (Table 10) was plotted against the average number of exclusion criteria, for each condition treated (Figure 4).

Table 10. Average Number of Exclusion Criteria Compared to Average Number of Chronic Conditions for Each Condition Treated

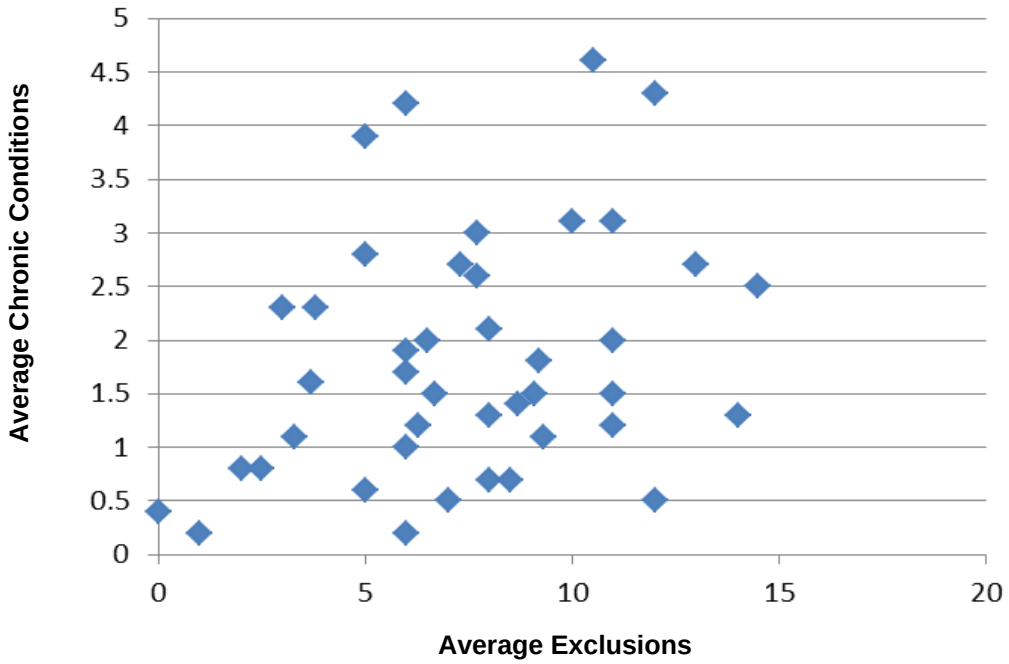
CONDITION TREATED	Average Exclusions	Average Chronic Conditions
Cystinosis	0.0	0.4
Contraception	1.0	0.2
Gaucher Disease	2.0	0.8
Cystic Fibrosis	2.5	0.8
Acute Coronary Syndrome	3.0	2.3
Neutropenia – Chemotherapy Induced	3.3	1.1
Diagnostic Imaging – CNS	3.7	1.6
Inflammatory Disorder of the Eye	3.8	2.3
Genital Warts	5.0	0.6
Infection – Skin	5.0	2.8
Pancreatic Insufficiency	5.0	3.9
Attention Deficit Hyperactivity Disorder	6.0	0.2
Fibromyositis	6.0	1.7
Gout	6.0	4.2
Human Immunodeficiency Virus	6.0	1.0
Pneumonia, Bacterial	6.0	1.9
Seizure Disorder	6.3	1.2
Neuropathy – Postherpetic	6.5	2.0
Malignant Neoplastic Disease	6.7	1.5
Infertility	7.0	0.5

[9]Vogeli C, Shields AE, Lee TA, Gibson TB, Marder WD, Weiss KB, Blumenthal D. Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. J Gen Intern Med 2007; 22(suppl 3):391–395.

[10] Loftis CW, Salinsky E. Medicare and mental health: The fundamentals. National Health Policy Forum, Background Paper, November 2006; 1-29.

CONDITION TREATED	Average Exclusions	Average Chronic Conditions
Renal Transplantation	7.3	2.7
Diabetes Mellitus	7.7	2.6
Postoperative Pain	7.7	3.0
Bipolar Disorder	8.0	0.7
Hypogonadism	8.0	2.1
Schizophrenia	8.0	1.3
Multiple Sclerosis	8.5	0.7
Psoriasis	8.7	1.4
Hypertensive Disorder	9.1	1.5
Obesity	9.2	1.8
Depressive Disorder	9.3	1.1
Gastrointestinal Ulcer	10.0	3.1
Idiopathic Pulmonary Fibrosis	10.5	4.6
Gastroesophageal Reflux Disease	11.0	1.5
Growth Hormone Deficiency	11.0	1.2
Osteoarthritis	11.0	2.0
Systemic Lupus Erythematosus	11.0	3.1
Neuropathy – Diabetic	12.0	4.3
Sexual Dysfunction	12.0	0.5
Hyperlipidemia	13.0	2.7
Viral Hepatitis	14.0	1.3
Low Back Pain	14.5	2.5

Figure 4. Comparison of the Average Number of Chronic Conditions to the Average Number of Exclusion Criteria for Each Condition Treated



The number of exclusions, surprisingly, had a weak positive correlation with the average number of chronic conditions in the subject medical history. Protocols having more exclusion criteria do not seem to necessarily result in a study population with fewer chronic conditions.

Because exclusion criteria do not influence the healthiness of the clinical trials population, other factors need to be considered in assessing whether subjects were appropriately enrolled or excluded. Table 11 presents the *conditions treated* that were associated with an average of 3 or more chronic conditions per subject and less than 1 chronic condition per subject.

Table 11. Average Number of Chronic Conditions per Subject by Condition Treated (≥ 3, < 1)

CONDITION TREATED	Average Number of Chronic Conditions
≥3	
Idiopathic Pulmonary Fibrosis	5
Gout	4
Neuropathy – Diabetic	4
Pancreatic Insufficiency	4
Diabetes Mellitus	3
Gastrointestinal Ulcer	3
Hyperlipidemia	3
Infection – Skin	3
Postoperative Pain	3

CONDITION TREATED	Average Number of Chronic Conditions
Renal Transplantation	3
Systemic Lupus Erythematosis	3
<1	
Gaucher Disease	0.8
Multiple Sclerosis	0.7
Genital Warts	0.6
Infertility	0.5
Sexual Dysfunction	0.5
Cystinosis	0.4
Attention Deficit Hyperactivity Disorder	0.2
Contraception	0.2

Studies where the target population was generally younger or ”healthier” (e.g., attention deficit hyperactivity disorder, contraception, infertility, genital warts) have fewer average numbers of chronic conditions compared to those diseases associated with additional comorbidities (e.g., idiopathic pulmonary fibrosis, diabetic neuropathy, hyperlipidemia, systemic lupus erythematosis). The current data do not allow consideration for the stage of disease targeted for intervention at the time of study enrollment. These observations are consistent with the hypothesis that the presence or absence of subjects with MCCs in clinical trials is more related to the population characteristics associated with the *condition treated* than it is to the protocol exclusion criteria. Further evaluation of these factors would require a model that also considers the appropriateness of subject exclusion for specific clinical trials.

5.3 Evaluation of Chronic Conditions Based on Study Exclusion Criteria

Individual exclusion criteria were compared to the percent of subjects with chronic conditions who were actually enrolled in studies. A subgroup analysis by age is also reported.

Across all study exclusions, hypertensive disease and dyslipidemia were the most frequent chronic conditions identified in the medical history records for the enrolled population. The presence of hypertensive disease ranged from 18.8% to 39.5%. Dyslipidemia was found in 16.6% to 43.9% of subjects. The finding was consistent for those ages <65 or 65+. Exclusion criteria did not preclude subjects with these two chronic conditions from entering the clinical trials examined for this project.

Chronic infectious disorders were the least frequent chronic condition across all exclusion criteria (0% to 0.6%), along with vascular disorder (0.5% to 1.5%). The other 16 chronic condition groups had a relatively low incidence in the clinical trial population.

As shown in Table 12, psychiatric disorder was an exclusion criterion in 113 studies; nevertheless, in studies overall, 11% to 23% of enrolled subjects had psychiatric disorder terms in their medical history documentation. Hepatic disorder exclusion was present in essentially the same number of studies (112 studies) but the prevalence in the medical histories was 0.6% to 2.8%.

Table 12. Comparison of Chronic Conditions Excluded and Percent of Subjects with Chronic Condition in Medical History for Psychiatric and Hepatic Disorders

Exclusion Criteria	Number of Studies (%) with Chronic Condition Excluded	Percent of Subjects with Chronic Condition in Medical History
Psychiatric Disorder	113 (76.9%)	11% to 23%
Hepatic Disorder	114 (77.6%)	0.6% to 2.8%

5.4 Evaluation of Chronic Conditions Based on Condition Treated

The percent of subjects with chronic conditions who were enrolled in the clinical trials was assessed in relation to each of the *conditions treated*.

Hypertension and dyslipidemia are frequent chronic conditions across many of the *conditions treated*. These are also the two most common chronic conditions in the middle-age and older study population. Subjects with *chronic infectious disease* and *vascular disorder* appear in relatively low percentages. The findings mirror those in Section 6.3 when evaluating the frequency of chronic conditions across exclusion criteria.

When one considers specific diseases with associated comorbidities, an additional question to consider is whether the enrolled subjects are ”healthier” than a comparable population due to exclusion of individuals with coexisting chronic conditions. The presence of associated chronic conditions when the *condition treated* was either hypertensive disease, diabetes mellitus, or hyperlipidemia was compared to the same combination of conditions in the overall database population, since a comparator group was not found in the literature (Table 13). Numbers in parentheses represent the co-occurrence of the two chronic conditions within the database population (the percent of subjects who had both conditions together in their medical history). Subjects enrolled in hypertensive disease studies, for example, would be expected to have a rate of *kidney disorder* similar to individuals having both *hypertensive disease* plus *kidney disorder* in their medical history.

Table 13. Percent of Associated Chronic Conditions with Select Conditions Treated

Condition Treated	Chronic Condition			
	Kidney Disorder	Vascular Disorder	Hypertensive Disease	Atherosclerotic Cardiovascular Disease
Hypertensive Disease	0.8% (5%)	0.8% (2.4%)	----	4.9% (30.7%)
Diabetes Mellitus	7.6% (3.7%)	8.4% (3.4%)	58.2% (48.2%)	16.1% (18.4%)
Hyperlipidemia	0.2% (4.3%)	0.4% (2.3%)	46.8% (46.6%)	5% (26.5%)

As shown in Table 13, clinical trials involving hypertensive disease and hyperlipidemia enrolled subjects that had a lower observed frequency of the comorbid conditions compared to the overall database population. Diabetes studies enrolled subjects with either equivalent or more comorbid conditions. The findings suggest that studies may have relatively “healthier” subjects enrolled.

5.5 Co-occurrence of Chronic Conditions

The term *multiple chronic conditions* implies the presence of at least 2 chronic conditions occurring in the same individual ("dyad"). The frequency of certain dyads is important from both a treatment and health care utilization perspective. Chronic condition dyads within the clinical trials database were assessed by looking at all possible combinations of chronic condition pairs and their frequency. For each defined chronic condition group, the presence of a co-occurring chronic conditions found in the subjects' medical history was assessed. Across all the defined conditions, hypertensive disease was most often associated with other chronic conditions (89.5%) followed by dyslipidemia (84.2%).

Table 14 presents the most frequent co-occurring chronic conditions within study subjects' medical histories, excluding the condition treated. Based upon the pathophysiology of the conditions, the pairs reflect what may be expected from a clinical perspective. While published data for these combinations are currently not available, other data sources may have the ability to compare clinical trials data with population statistics to assess if subjects with MCCs are represented in clinical trials.

Table 14. Most Frequent Co-Occurring Chronic Conditions within Study Subjects' Medical Histories

	Chronic Condition 1	Chronic Condition 2	Percent
1	Atherosclerotic Cardiovascular Disease	Hypertensive Disease	70.4%
2	Kidney Disorder	Hypertensive Disease	68.6%
3	Vascular Disorder	Hypertensive Disease	65.0%
4	Heart Disorder	Hypertensive Disease	58.1%
5	Vascular Disorder	Dyslipidemia	54.0%
6	Atherosclerotic Cardiovascular Disease	Dyslipidemia	53.7%
7	Dyslipidemia	Hypertensive Disease	52.8%
8	Kidney Disorder	Dyslipidemia	52.1%
9	Heart Disorder	Dyslipidemia	50.4%
10	Diabetes Mellitus	Hypertensive Disease	48.2%

5.6 Case Studies

Two case studies explored specific questions regarding potential exclusion of subjects from clinical trials.

5.6.1 Case Study 1

Psychiatric disorder was an exclusion in 76.9% of clinical trials in the study database. To evaluate the extent to which subjects with psychiatric disorder were actually being excluded, clinical trials of psychiatric disorders were not used from the database. The remaining studies were evaluated for the percent of subjects having psychiatric disorder in their medical history. As indicated in Table 15, there was a wide range of values across the various conditions treated (2.8% to 82.4%) with an

overall occurrence of 3.9%. No specific pattern was observed. Comparative published data for these groups were not available.

Table 15. Percent of Subjects with Psychiatric Disorder by Condition Treated

Condition Treated	Percent of Subjects with Psychiatric Disorder
Infection – Skin	82.4
Pancreatic Insufficiency	46.2
Viral Hepatitis	34.5
Hyperlipidemia	31.6
Gastrointestinal Ulcer	30.3
Low Back Pain	29.4
Postoperative Pain	27.0
Gout	24.9
Seizure Disorder	24.7
Idiopathic Pulmonary Fibrosis	24.5
Systemic Lupus Erythematosus	23.9
Human Immunodeficiency Virus	23.4
Neuropathy – Diabetic	22.8
Fibromyositis	20.5
Gastroesophageal reflux disease	20.3
Multiple Sclerosis	19.6
Hypogonadism	19.4
Malignant Neoplastic Disease	18.9
Osteoarthritis	17.3
Psoriasis	16.0
Inflammatory Disorder of the Eye	15.7
Diagnostic Imaging – CNS	14.6
Obesity	14.4
Acute Coronary Syndrome	14.3
Renal Transplantation	14.2
Neuropathy – Postherpetic	13.4
Hypertensive Disorder	12.0
Genital Warts	11.8
Growth Hormone Deficiency	11.8
Infertility	11.1
Cystic Fibrosis	8.7
Diabetes Mellitus	7.8
Pneumonia – Bacterial	7.8
Neutropenia – Chemotherapy Induced	6.5
Contraception	6.2

Condition Treated	Percent of Subjects with Psychiatric Disorder
Sexual Dysfunction	5.2
Cystinosis	2.8

5.6.2 Case Study 2

A history of cardiovascular disease (defined for this Case Study as atherosclerotic coronary vascular disease, heart disorder, and hypertensive disease) may pose additional risk for clinical trial subjects. Cardiovascular disease studies were removed from the analysis and the remaining clinical trials evaluated for the prevalence of cardiovascular disease in the subjects' medical histories. As in Case Study 1, a large range of cardiovascular disease history was observed, 4.4% to 88.5% with an overall average of 33.9%. Within a group of studies that would fall under the same chronic condition category, e.g., psychiatric disorder, the occurrence of cardiovascular disease was fairly consistent: bipolar disorder (17.8%), depressive disorder (18.2%), and schizophrenia (19.6%). Table 16 provides details concerning the prevalence of cardiovascular disease in subjects' medical histories. However, no comparable published data were available to measure this finding in relation to the general population.

Table 16. Percent of Subjects with a Prevalence of Cardiovascular Disease in Their Medical Histories by Condition Treated

Condition Treated	Cardiovascular Disease	Atherosclerotic Cardiovasacular Disease	Heart Disorder	Hypertensive Disease
All	33.9	6.0	6.7	29.6
Attention Deficit Hyperactivity Disorder	4.4	0.0	4.4	0.0
Bipolar Disorder	17.8	0.0	0.6	17.5
Contraception	1.0	0.1	0.3	0.7
Cystic Fibrosis	3.4	0.0	2.1	1.3
Cystinosis	5.6	0.0	2.8	2.8
Depressive Disorder	18.2	1.1	4.4	13.9
Diabetes Mellitus	63.9	16.1	8.1	58.2
Diagnostic Imaging – CNS	27.4	7.1	4.6	23.2
Fibromyositis	24.7	1.1	6.3	19.4
Gastroesophageal Reflux Disease	31.1	4.6	5.8	26.9
Gastrointestinal Ulcer	45.5	4.7	7.7	41.4
Gaucher Disease	39.4	0.0	33.3	12.1
Gential Warts	11.0	1.0	1.3	10.0
Gout	76.9	19.6	32.4	70.7
Growth Hormone Deficiency	19.7	5.3	1.3	15.1
Human Immunodeficiency Virus	14.7	1.8	3.4	11.3
Hyperlipidemia	53.6	5.0	11.4	46.8

Condition Treated	Cardiovascular Disease	Atherosclerotic Cardiovasacular Disease	Heart Disorder	Hypertensive Disease
Hypogonadism	40.7	5.2	5.2	35.5
Idiopathic Pulmonary Fibrosis	65.9	27.0	21.3	53.8
Infection – Skin	39.2	22.6	10.5	29.7
Infertility	5.5	0.0	3.3	2.2
Inflammatory Disorder of the Eye	49.5	8.3	9.1	46.1
Low Back Pain	41.7	6.7	7.3	38.2
Malignant Neoplastic Disease	36.7	8.3	6.8	30.1
Multiple Sclerosis	9.0	0.5	2.5	6.4
Neuropathy – Diabetic	80.4	27.7	16.6	75.3
Neuropathy – Postherpetic	56.0	13.2	7.1	38.2
Neutropenia – Chemotherapy Induced	36.8	15.3	5.0	29.7
Obesity	34.7	1.6	5.9	31.4
Osteoarthritis	51.5	9.4	9.3	46.8
Pancreatic Insufficiency	61.5	10.3	18.0	48.7
Pneumonia – Bacterial	56.2	28.6	27.6	45.7
Postoperative Pain	54.0	8.4	14.5	48.7
Psoriasis	29.5	3.6	2.7	27.6
Renal Transplantation	88.5	13.0	23.1	86.4
Schizophrenia	19.6	1.1	2.0	17.5
Seizure Disorder	15.5	4.7	2.6	11.3
Sexual Dysfunction	7.0	0.1	3.5	3.7
Systemic Lupus	38.1	6.1	10.8	30.2
Viral Hepatitis	23.7	2.1	4.3	20.3

6 Project Limitations

The findings presented in this report have several limitations in terms of data availability and aggregation of medical terms into chronic condition groups. These are described in more detail below.

6.1 Availability of Screening Data

Data on subjects who were screened, but not enrolled, are not submitted to FDA.

The current database includes only enrolled subjects and therefore cannot reflect the complete scope of excluded subjects, and whether those subjects were excluded on the basis of MCCs or other reasons.

6.2 Defining Chronic Conditions and Standardized Terminology

The SNOMED dictionary was used to standardize and combine medical history and exclusion information into a list of chronic conditions. Different levels of the SNOMED hierarchy were used to retain more specificity around some specific conditions of interest, while others were grouped into broader categories. Based upon the clinical judgment of the project TAG, some terms and procedures were moved to different groupings to reflect common clinical practices.

6.3 Medical History Data

Investigators are usually not required to use standard terminology and diagnoses in medical history forms. The result is that a large amount of manual interpretation and coding is required to standardize the data for analysis. Medical history is a significant record of the subject profile entering a clinical trial.

7 Data Limitations

7.1 Data Format

Approximately 40% of the subject-level raw data retrieved for the project were not standardized to a common format such as SDTM. The structure for this data was unique to the sponsor, and often varied within an NDA/BLA. This required mapping each study's data definition to the project's standard SDTM structure for the retrieved subject-level demographic and medical history data for approximately 60 of the 147 studies included in the database.

7.2 Exclusion Criteria Format

Approximately 50% of the study-level exclusion criteria retrieved for the project were submitted as text files rather than SDTM-formatted, electronic files. The process for converting the data into an analyzable format required manually pasting text from the CSR into a spreadsheet and then formatting it into the project's SDTM format for approximately 75 of the 147 studies included in the database.

7.3 ClinicalTrials.gov

ClinicalTrials.gov proved to be a peripheral data source for the project. Typically the data retrieved from ClinicalTrials.gov was less up-to-date or discrepant in comparison with the final study protocol and completed study data submitted to the FDA. The most reliable data found in ClinicalTrials.gov were the Study NCT Number and study design elements. ClinicalTrials.gov was most useful during the data retrieval phase of the project in helping to identify the appropriate studies in the FDA submission systems by providing the study identifiers used by the sponsor.

8 Discussion

The question of whether individuals with MCCs are systematically *excluded* from controlled clinical trials can only be answered indirectly from existing data, because analysis of the enrolled subjects only provide an indication of *inclusion* rates. The absence of subject screening logs limits insight to the specific reasons for enrollment rejection. The current project considers two measures

to assess the inclusion of subjects with MCCs: 1) the presence of specific exclusions in the clinical trial protocols, 2) the actual enrolled subjects, examining the frequency of MCCs.

The 147 studies in the current database covered 42 different conditions treated. The five most frequent conditions treated were hypertensive disorder, diabetes mellitus, malignant neoplastic disease, obesity, and psoriasis. There was a broad range of exclusion criteria across the studies (0–16) with an average of 7.9.

MCCs increase with age. Older paitents were somewhat overrepresented in the database, as 19% of the database population was 65 years of age or older, compared to 14% of the general US population. Other trends were assessed within the database population to further determine if it was a representative sample. The number of chronic conditions increased across the age bands, and a shift in the specific prevalence of specific conditions also paralleled that of the general population. The percent of subjects having hypertension, dyslipidemia, atherosclerotic cardiac disease, and arthritis and arthropathy increased with age. Individuals with ≥1 and ≥2 chronic conditions also were comparable to published reports. Women under 65 years old generally have more chronic conditions than men, but this trend reverses in the 65+ group of subjects. The current project database of clinical trials appears generally consistent with respect to population chronic condition trends. However, comparison of the absolute occurrence for certain conditions demonstrated some differences.

Whenever available, published data on the prevalence of chronic conditions in the general population were utilized as a benchmark to evaluate the possible exclusion of subjects with chronic conditions in clinical trials. Most of the literature focuses on the Medicare population, where there are more frequent chronic conditions. The occurrence of three chronic condition groups was notably different from the Medicare population figures: (1) arthritis and arthropathy (19% in the database versus 57% in literature), (2) pulmonary disorder (13% versus 38%), and (3) psychiatric disorder (11% versus 26%).[11,12] Psychiatric disorder was the second most common exclusion criterion, found in three quarters of clinical studies for non-psychatric indications. A tendency to enroll "healthier" subjects in certain trials was also observed. Hypertension, diabetes, and hyperlipidemia may be associated with kidney disorder, vascular disorder, and atherosclerotic cardiovascular disease. The occurrence of the latter 3 comorbid conditions, for subjects enrolled in hypertension, diabetes, or hyperlipidemia trials, was compared to the occurrence of the same pair of conditions in the overall database population, since no matching published comparators were found for the general population. Clinical trials of hypertension and hyperlipidemia enrolled subjects that had a lower frequency of the comorbid conditions compared to the overall project database. Diabetes trials enrolled subjects who had a higher or comparable number of comorbid conditions to the overall clinical trial population. Protocol exclusion criteria are a significant element in excluding subjects from clinical trials; however, they may not be the only factor.

The fact that a protocol imposes a large number of exclusion criteria does not necessarily mean that enrolled subjects will have few chronic conditions. In fact, the current data show a weak, positive correlation such that more exclusions are associated with an increased number of chronic conditions per subject. The presence or absence of subjects with MCCs in clinical trials is not only

[11] Vogeli, 392.

[12] Loftis, 4.

determined by exclusion criteria, but also by the population characteristics associated with the condition treated and stage of disease targeted for therapeutic intervention. Clinical trials focusing on multisystem diseases tended to have the highest average number of chronic conditions per subject (e.g., diabetic neuropathy, idiopathic pulmonary fibrosis, diabetes mellitus) whereas those diseases that occur in a younger or healthier population had fewer chronic conditions per subject (e.g., infertility, contraception, genital warts). Further investigation on the appropriateness of excluding patients with MCCs from lcnical trials is needed.

Observations from the current database have included specific chronic conditions and trends for multiple chronic conditions. An analysis of the most frequent co-occurring chronic conditions finds that atherosclerotic cardiovascular disease plus hypertensive disease occurred in 70.4% of subjects. There are no published data to directly compare chronic condition dyads with the general population data. However, to fully assess the presence or absence of MCCs in clinical trials, it would be necessary to identify sources for this type of data. Future research may use the CMS database as a reference population.

Analysis of 147 studies from NDAs and BLAs submitted to FDA in FY2010 supports two primary findings:

- Analysis of the study-level inclusion-exclusion criteria shows substantial variation in the number of exclusions per study by therapeutic indication. In particular, subjects with hepatic disorders, psychiatric disorder, and neoplasms tended to be excluded from the clinical trials. Of these, exclusions for hepatic disorder and neoplasm are not surprising in a clinical trials context. These exclusions did not result, however, in a population with a low rate of chronic conditions, although certain conditions were less frequently observed than in the case of the Medicare population. Exclusion of patients with psychiatric disorders may be a particular concern, if many drugs have psychiatric effects, and these exclusions deserve further study.
- Full analysis of the frequency of chronic conditions of patients enrolled in clinical trials was not possible without information the prevalence of chronic conditions in an age-corrected population. Nonetheless, some diseases groupings, such as psychiatric and pulmonary diseases, appear to have a substantially lower prevalence in the clinical trials population than the expected prevalence in an age-corrected population. Somewhat lower percentages in a clinical trials context may not be problematic as long as patients with multiple chronic conditions are represented.

Appendix 1—Chronic Conditions and Associated FSN Terms in Each Category

Chronic Condition	SNOMED FSN
Arthritis & Arthropathy	Arthritis (Disorder)
Arthritis & Arthropathy	Arthropathy (Disorder)
Arthritis & Arthropathy	Disseminated Idiopathic Skeletal Hyperostosis (Disorder)
Arthritis & Arthropathy	Osteoarthritis (Disorder)
Arthritis & Arthropathy	Rheumatoid Arthritis (Disorder)
At Risk For Injury	At Risk For Injury (Finding)
At Risk For Injury	Onset Of Illness (Finding)
Atherosclerotic Cardiovascular Disease	Angina (Disorder)
Atherosclerotic Cardiovascular Disease	Arteriosclerotic Vascular Disease (Disorder)
Atherosclerotic Cardiovascular Disease	Cerebrovascular Accident (Disorder)
Atherosclerotic Cardiovascular Disease	Cerebrovascular Disease (Disorder)
Atherosclerotic Cardiovascular Disease	Coronary Angioplasty (Procedure)
Atherosclerotic Cardiovascular Disease	Coronary Arteriosclerosis (Disorder)
Atherosclerotic Cardiovascular Disease	Coronary Artery Bypass Grafting (Procedure)
Atherosclerotic Cardiovascular Disease	Diabetic Peripheral Angiopathy (Disorder)
Atherosclerotic Cardiovascular Disease	Intermittent Claudication (Disorder)
Atherosclerotic Cardiovascular Disease	Ischemic Heart Disease (Disorder)
Atherosclerotic Cardiovascular Disease	Myocardial Infarction (Disorder)
Atherosclerotic Cardiovascular Disease	Peripheral Vascular Disease (Disorder)
Atherosclerotic Cardiovascular Disease	Preinfarction Syndrome (Disorder)
Atherosclerotic Cardiovascular Disease	Renal Artery Stenosis (Disorder)
Autoimmune Disorder	Antiphospholipid Syndrome (Disorder)
Autoimmune Disorder	Disorder Of Connective Tissue (Disorder)
Autoimmune Disorder	Dry Eye (Finding)
Autoimmune Disorder	Graves' Disease (Disorder)
Autoimmune Disorder	Lupus Erythematosus (Disorder)
Autoimmune Disorder	Psoriasis (Disorder)
Autoimmune Disorder	Psoriasis With Arthropathy (Disorder)

Chronic Condition	SNOMED FSN
Autoimmune Disorder	Sjögren's Syndrome (Disorder)
Chronic Infectious Disorder	Acquired Immune Deficiency Syndrome (Aids) (Disorder)
Chronic Infectious Disorder	Human Immunodeficiency Virus (Organism)
Chronic Infectious Disorder	Human Papilloma Virus Infection (Disorder)
Diabetes Mellitus	Diabetes Mellitus (Disorder)
Diabetes Mellitus	Diabetes Mellitus Type 1 (Disorder)
Diabetes Mellitus	Diabetes Mellitus Type 2 (Disorder)
Dyslipidemia	Dyslipidemia (Disorder)
Dyslipidemia	Hypercholesterolemia (Disorder)
Dyslipidemia	Hyperlipidemia (Disorder)
Dyslipidemia	Hyperlipoproteinemia (Disorder)
Dyslipidemia	Hypertriglyceridemia (Disorder)
Dyslipidemia	Serum Triglycerides Raised (Finding)
Endocrine/metabolic Disorder	Addison's Disease (Disorder)
Endocrine/metabolic Disorder	Adrenal Cortical Hypofunction (Disorder)
Endocrine/metabolic Disorder	Autoimmune Thyroiditis (Disorder)
Endocrine/metabolic Disorder	Disorder Of Thyroid Gland (Disorder)
Endocrine/metabolic Disorder	Glucose-6-Phosphate Dehydrogenase Deficiency Anemia (Disorder)
Endocrine/metabolic Disorder	Glycogen Storage Disease, Muscular Form (Disorder)
Endocrine/metabolic Disorder	Growth Hormone Deficiency (Disorder)
Endocrine/metabolic Disorder	Hormone Abnormality (Finding)
Endocrine/metabolic Disorder	Hyperparathyroidism (Disorder)
Endocrine/metabolic Disorder	Hyperthyroidism (Disorder)
Endocrine/metabolic Disorder	Hypoparathyroidism (Disorder)
Endocrine/metabolic Disorder	Hypothyroidism (Disorder)
Endocrine/metabolic Disorder	Metabolic Acidosis (Disorder)
Endocrine/metabolic Disorder	Obese (Finding)
Endocrine/metabolic Disorder	Osteoporosis (Disorder)
Endocrine/metabolic Disorder	Pituitary-Dependent Cushing's Disease (Disorder)

Chronic Condition	SNOMED FSN
Endocrine/metabolic Disorder	Thyroid Function Tests Abnormal (Finding)
Gastrointestinal Disorder	Celiac Disease (Disorder)
Gastrointestinal Disorder	Colitis (Disorder)
Gastrointestinal Disorder	Crohn's Disease (Disorder)
Gastrointestinal Disorder	Disorder Of Gastrointestinal Tract (Disorder)
Gastrointestinal Disorder	Gastritis (Disorder)
Gastrointestinal Disorder	Gastroesophageal Reflux Disease (Disorder)
Gastrointestinal Disorder	Pancreatitis (Disorder)
Genitourinary Disorder	Benign Prostatic Hyperplasia (Disorder)
Genitourinary Disorder	Genuine Stress Incontinence (Finding)
Genitourinary Disorder	Urinary Incontinence (Finding)
Heart Disorder	Abnormal Cardiac Conduction (Finding)
Heart Disorder	Atrial Fibrillation (Disorder)
Heart Disorder	Atrial Flutter (Disorder)
Heart Disorder	Atrioventricular Block (Disorder)
Heart Disorder	Cardiomyopathy (Disorder)
Heart Disorder	Congestive Heart Failure (Disorder)
Heart Disorder	Disorder Of Cardiac Function (Disorder)
Heart Disorder	Electrocardiogram Abnormal (Finding)
Heart Disorder	Heart Valve Disorder (Disorder)
Heart Disorder	Heart Valve Replacement (Procedure)
Heart Disorder	Hypertrophic Cardiomyopathy (Disorder)
Heart Disorder	Left Atrial Abnormality (Disorder)
Heart Disorder	Procedure On Coronary Arteries (Procedure)
Heart Disorder	Prolonged Qt Interval (Finding)
Heart Disorder	Ventricular Hypertrophy (Disorder)
Hepatic Disorder	Abnormal Liver Function (Finding)
Hepatic Disorder	Chronic Hepatitis (Disorder)
Hepatic Disorder	Disorder Of Liver (Disorder)
Hepatic Disorder	Hepatitis B And Hepatitis C (Disorder)
Hepatic Disorder	Hepatitis B Surface Antigen Positive (Finding)

Chronic Condition	SNOMED FSN
Hepatic Disorder	Hepatitis C Antibody Test Positive (Finding)
Hepatic Disorder	Hyperbilirubinemia (Disorder)
Hepatic Disorder	Inflammatory Disease Of Liver (Disorder)
Hepatic Disorder	Liver Cyst (Disorder)
Hepatic Disorder	Liver Enzymes Abnormal (Finding)
Hepatic Disorder	Type B Viral Hepatitis (Disorder)
Hepatic Disorder	Viral Hepatitis C (Disorder)
Hypertensive Disease	Hypertensive Disorder, Systemic Arterial (Disorder)
Hypertensive Disease	Hypertensive Encephalopathy (Disorder)
Kidney Disorder	Cystic Disease Of Kidney (Disorder)
Kidney Disorder	Diabetic Renal Disease (Disorder)
Kidney Disorder	End Stage Renal Disease (Disorder)
Kidney Disorder	Kidney Disease (Disorder)
Kidney Disorder	Renal Function Tests Abnormal (Finding)
Kidney Disorder	Renal Impairment (Disorder)
Multisystem Disorder	Asthenia (Finding)
Multisystem Disorder	Behcet's Syndrome (Disorder)
Multisystem Disorder	Chronic Fatigue Syndrome (Disorder)
Multisystem Disorder	Degenerative Disorder (Disorder)
Multisystem Disorder	Ehlers-Danlos Syndrome (Disorder)
Multisystem Disorder	Fibromyositis (Disorder)
Multisystem Disorder	Sarcoidosis (Disorder)
Neoplasm	Malignant Neoplastic Disease (Disorder)
Neurological Disorder	Abnormal Involuntary Movement (Disorder)
Neurological Disorder	Akathisia (Disorder)
Neurological Disorder	Alzheimer's Disease (Disorder)
Neurological Disorder	Amnestic Disorder (Disorder)
Neurological Disorder	Ataxia (Finding)
Neurological Disorder	Cerebral Degeneration (Disorder)
Neurological Disorder	Chronic Organic Mental Disorder (Disorder)
Neurological Disorder	Cluster Headache Syndrome (Disorder)

Chronic Condition	SNOMED FSN
Neurological Disorder	Delirium (Disorder)
Neurological Disorder	Dementia (Disorder)
Neurological Disorder	Disorder Of Nervous System (Disorder)
Neurological Disorder	Disturbance Of Consciousness (Finding)
Neurological Disorder	Generalized Seizure (Finding)
Neurological Disorder	Impaired Cognition (Finding)
Neurological Disorder	Injury Of Head (Disorder)
Neurological Disorder	Migraine (Disorder)
Neurological Disorder	Movement Disorder (Disorder)
Neurological Disorder	Multiple Sclerosis (Disorder)
Neurological Disorder	Neuropathy (Disorder)
Neurological Disorder	Parkinsonism (Disorder)
Neurological Disorder	Parkinson's Disease (Disorder)
Neurological Disorder	Seizure Disorder (Disorder)
Neurological Disorder	Tardive Dyskinesia (Disorder)
Psychiatric Disorder	Adjustment Disorder (Disorder)
Psychiatric Disorder	Agoraphobia (Disorder)
Psychiatric Disorder	Alcohol Abuse (Disorder)
Psychiatric Disorder	Anorexia Nervosa (Disorder)
Psychiatric Disorder	Anxiety Disorder (Disorder)
Psychiatric Disorder	Attention Deficit Hyperactivity Disorder (Disorder)
Psychiatric Disorder	Bipolar Disorder (Disorder)
Psychiatric Disorder	Bulimia Nervosa (Disorder)
Psychiatric Disorder	Depressive Disorder (Disorder)
Psychiatric Disorder	Drug Abuse (Disorder)
Psychiatric Disorder	Drug-Induced Tardive Dystonia (Disorder)
Psychiatric Disorder	Eating Disorder (Disorder)
Psychiatric Disorder	Generalized Anxiety Disorder (Disorder)
Psychiatric Disorder	Mental Disorder (Disorder)
Psychiatric Disorder	Mixed Anxiety And Depressive Disorder (Disorder)
Psychiatric Disorder	Obsessive-Compulsive Disorder (Disorder)

Chronic Condition	SNOMED FSN
Psychiatric Disorder	Posttraumatic Stress Disorder (Disorder)
Psychiatric Disorder	Psychotic Disorder (Disorder)
Psychiatric Disorder	Schizoaffective Disorder (Disorder)
Psychiatric Disorder	Schizophrenia (Disorder)
Psychiatric Disorder	Substance Abuse (Disorder)
Pulmonary Disorder	Asthma (Disorder)
Pulmonary Disorder	Asthmatic Bronchitis (Disorder)
Pulmonary Disorder	Bronchitis (Disorder)
Pulmonary Disorder	Chronic Obstructive Lung Disease (Disorder)
Pulmonary Disorder	Sleep Apnea (Disorder)
Vascular Disorder	Chronic Pulmonary Heart Disease (Disorder)
Vascular Disorder	Cor Pulmonale (Disorder)
Vascular Disorder	Diabetic Retinopathy (Disorder)
Vascular Disorder	Disorder Of Cardiovascular System (Disorder)
Vascular Disorder	Disorder Of Carotid Artery (Disorder)
Vascular Disorder	History Of Cardiovascular Surgery (Situation)
Vascular Disorder	Peripheral Pulmonary Artery Disease (Disorder)
Vascular Disorder	Pulmonary Hypertension (Disorder)

Appendix 2—Conditions Treated and Their Frequency

Condition Treated	Frequency	Percentage of Total Studies
Acute Coronary Syndrome	1	0.7%
Attention Deficit Hyperactivity Disorder	1	0.7%
Bipolar Disorder	1	0.7%
Contraception	2	1.4%
Cystic Fibrosis	2	1.4%
Cystinosis	1	0.7%
Depressive Disorder	3	2.0%
Diabetes Mellitus	14	9.5%
Diagnostic Imaging - CNS	3	2.0%
Fibromyositis	2	1.4%
Gastoesophageal reflux disease	4	2.7%
Gastrointestinal Ulcer	2	1.4%
Gaucher Disease	1	0.7%
Genital Warts	2	1.4%
Gout	2	1.4%
Growth Hormone Deficiency	1	0.7%
Human immunodeficiency virus	4	2.7%
Hyperlipidemia	1	0.7%
Hypertensive Disorder	20	13.6%
Hypogonadism	1	0.7%
Idiopathic Pulmonary Fibrosis	2	1.4%
Infection - Skin	2	1.4%
Infertility	1	0.7%
Inflammatory disorder of the eye	5	3.4%
Low Back Pain	2	1.4%
Malignant Neoplastic Disease	13	8.8%
Multiple Sclerosis	2	1.4%
Neuropathy - Diabetic	1	0.7%
Neuropathy - Postherpetic	2	1.4%

Condition Treated	Frequency	Percentage of Total Studies
Neutropenia - chemotherapy induced	3	2.0%
Obesity	9	6.1%
Osteoarthritis	5	3.4%
Pancreatic Insufficiency	1	0.7%
Pneumonia, bacterial	2	1.4%
Postoperative Pain	3	2.0%
Psoriasis	6	4.1%
Renal Transplantation	4	2.7%
Schizophrenia	4	2.7%
Seizure Disorder	3	2.0%
Sexual Dysfunction	5	3.4%
Systemic Lupus Erythematosus	2	1.4%
Viral Hepatitis	2	1.4%
TOTAL STUDIES	**147**	**100.00%**

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