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Hypersensitivity Adverse Event Reporting in Clinical Cancer Trials: Barriers and Potential Solutions to Studying Severe Events on a Population Level

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HYPERSENSITIVITY ADVERSE EVENT REPORTING IN CLINICAL CANCER TRIALS: BARRIERS AND POTENTIAL SOLUTIONS TO STUDYING SEVERE EVENTS ON A POPULATION LEVEL

by

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ABSTRACT

HYPERSENSITIVITY ADVERSE EVENT REPORTING IN CLINICAL CANCER TRIALS: BARRIERS AND POTENTIAL SOLUTIONS TO STUDYING ALLERGIC EVENTS ON A POPULATION LEVEL
by

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Clinical cancer trial interventions are associated with hypersensitivity events (HEs) which are recorded in the national clinical trial registry, ClinicalTrials.gov and publicly available. This data could potentially be leveraged to study predictors for HEs to identify at risk patients who may benefit from desensitization therapies to prevent these potentially life-threatening reactions. However, variation in investigator reporting methods is a barrier to leveraging this data for aggregation and analysis. The National Cancer Institute has developed the CTCAE classification system to address this barrier. This study analyzes the comprehensiveness of CTCAE to describe severe HEs in clinical cancer trials in comparison to other systems or terminologies.

An XML parser was used to extract readable text from adverse event tables. Queries of the parsed data elements were performed to identify immune disorder events associated with biological and chemotherapy interventions. A data subset of severe anaphylactic and anaphylactoid events was created and analyzed.

1,331 clinical trials with 13088 immune disorder events occurred from September 20, 1999 to March 2018. 2409 (18.4%) of these were recorded as “serious” events. In the severe subset, MedDRA terminology, CTCAE or CTC classification systems were used to describe HEs,

however, a large number of studies did not specify the system. The CTCAE term “anaphylaxis” was miscoded as “other (not including serious)” in 76.2% of events. The CTCAE classification system severity grades levels were not used to describe any of the severe events and the majority of terms did not include the allergen and therefore, in dual or multi- drug therapies, the etiologic agent was not identifiable. Furthermore, collection methods were not specified in 76% of events.

Therefore, CTCAE was not found to improve the ability to capture event etiology or severity in anaphylaxis and anaphylactoid events in cancer clinical trials. Potential solutions to improving CTCAE HE description include adapting terms with a low percentage of HE severity miscoding (e.g. anaphylactic reaction) and terms which include drugs, biological agents and/or drug classes to improve study of anaphylaxis etiology and incidence in multi-drug cancer therapy, therefore, making a significant impact on patient safety.

Dedication Page

To

Dr. Timothy Patrick,

without your mentorship,

this would not have been possible, your insight and support for students should be emulated

throughout the field of Biomedical and Health Informatics

and

to my Mom, Judy Eldredge,

who inspired this work

and

to all the members of my Committee,

thank you for your endless support!

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CHAPTER ONE: INTRODUCTION

This study aims to analyze the feasibility to study severe hypersensitivity events secondary to clinical cancer trial drug and biological agent interventions, identify barriers to conducting population-level analysis of these adverse events, and suggest potential practical solutions to address the barriers. A preliminary analysis of publicly available data in clinicaltrails.gov revealed significant challenges to population-level analysis of hypersensitivity events across clinical trials due to variation in clinical trial reporting data collection methods, lack of information on the etiology (antigen) of the event, temporal information, and lack of granularity (lower level terms) available to code hypersensitivity allergic events in certain controlled terminologies and classification systems. Furthermore, the complex nature of cancer interventions with several drugs and/or agents involved in one clinical trial arm compounded the problem of characterizing the hypersensitivity events. The National Cancer Institute has developed five severity "grade" levels with their Common Terminology Criteria for Adverse Events (CTCAE) classification system (National Cancer Institute, 2006) to address this barrier, however, the preliminary analysis of the data revealed that these grades are not regularly used in reporting hypersensitivity events in this dataset. (Eldredge, Singavi, Lam, Gallagher, & Luo, 2018) Furthermore, the literature notes the unique challenges of using controlled terminology or classification systems to capture hypersensitivity events, especially allergic events. (Goss, et al., 2013) Therefore, it is hypothesized that lack of granularity with regards to documenting the antigen and accurate identification of severity in adverse hypersensitivity event reporting in dual and multi drug and/or biological agent therapy interventions hinders the ability to identify and study the incidence of these events, specifically in a case study of severe anaphylaxis and anaphylactoid reactions with cancer therapy interventions, across clinical trials.

To test this theory, this study will first analyze the current state of hypersensitivity adverse event reporting in cancer clinical therapy using data from clinicaltrials.gov. The scope of the study will be focused on hypersensitivity events which are categorized as immune disorder events by the National Cancer Institute (NCI) and a case study of a subset of severe hypersensitivity adverse events, specifically anaphylactic and anaphylactoid events which are severe immediate life-threatening adverse events. Variation in terminology use and gaps in reporting the antigen etiology (referred to as "allergen" in reference to purely allergic events in this study) and adverse event severity will be analyzed to inform future secondary use of the data for population level analysis, future terminology or classification system improvements, and semantic mapping of hypersensitivity events.

Cancer incidence is increasing and may surpass diseases of the heart as the most common cause of death in the United States (National Vital Statistics, 2017). New initiatives, such as the National Cancer Institute Cancer Moonshot, aim to expedite and streamline research to find a cure for this devastating disease (Institute, 2018). As a result, several new anti-cancer therapies are being approved by the U.S. Federal Food and Drug Administration through a "fast track process" (U.S. Food & Drug Administration, 2018). Furthermore, new research and development is increasing the number of available drugs and therapies, especially biological immune therapies. However, cancer therapy, especially chemotherapy and biological therapies, are known to be associated with severe adverse events, especially severe hypersensitivity events, often referred to anaphylaxis or anaphylactoid reactions. (Giavina-Bianchi, Patil, & Banerji, 2017). Despite this, few predictive risk factors are known, however, several possible risk factors

for severe anaphylactic reactions are being studied such as age, gender, vigorous exercise and certain drugs and biological agents. (Worm, et al., 2018) Furthermore, new methods for treatment such as drug desensitization therapy can be used to prevent these potentially life-threatening events, however, prior risk identification would inform potential candidates. (Bonamichi-Santos & Castells, 2018)

ClinicalTrails.gov is one of the largest databases of clinical trial data, both publicly and privately funded. (ClinicalTrials.gov, 2018) This registry has steadily grown since the year 2000, incorporating increasing requirements for clinical trial outcomes and adverse event reporting. Currently, all adverse events, including hypersensitivity events, in ClinicalTrails.gov, are recorded by the clinical trial investigator team using their collection assessment method and terminology or classification system of choice. (U.S. National Library of Medicine, 2017) Since investigators vary in their data collection assessment methods and choice of controlled terminology for data reporting, significant barriers exist to the secondary analysis of this data on a population level to support studies on risks factors for hypersensitivity events in cancer trials. In addition, the comprehensiveness of each terminology, to capture allergy event severity, allergen, acuteness and recurrence varies significantly, compounding the problem. (Goss et al, 2013) In this study, adverse allergic events were extracted from semi-structured tables in ClinicalTrials.gov from the time period of 1999 through 2018 using an XML parser. The terminology used to describe these events was analyzed for the presence of descriptors specifically: allergen, severity, acuteness and reoccurrence. Additionally, the collection and assessment method used by each investigator was examined.

The following research questions and hypotheses was used in analyzing the data:

Research Question:

Is the use of National Cancer Institute CTCAE Classification System, with its ability to grade severity of adverse events, improving the ability to aggregate clinical trial data to study the incidence, etiology and severity of severe hypersensitivity events secondary to cancer biological and/or chemotherapeutic agents on a population level (across clinical trials) in comparison to the use of MedDRA?

Hypothesis #1*:*

The ability to accurately record severity of anaphylactic and anaphylactoid events secondary to cancer biological and/or chemotherapy agents is improving with the use of the CTCAE classification system and its emphasis on severity grades in comparison to MedDRA.

Hypothesis #2:

Terms used to describe severe anaphylactic and anaphylactoid events recorded in the dataset of clinical cancer trials from ClinicalTrials.gov rarely (<5% of events) include the antigen responsible for the event which hinders the ability to study incidence of drug and biological agent induced hypersensitivity events when the clinical trial intervention includes multiple drugs and/or multiple therapeutic agents. In other words, there is no statistical difference between the types of terminologies or classification systems used regarding the inclusion of the antigen within the severe hypersensitivity event term.

Hypothesis #3:

Over 25% of the severe anaphylactic and anaphylactoid events have not been recorded using a systematic assessment method which could result in underreporting of events.

CHAPTER TWO: BACKGROUND AND LITERATURE REVIEW

Definitions and classification of adverse drug reactions

Adverse drug reactions (ADRs) fall under adverse drug events (AEs). The FDA Guideline for Industry, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting", defines as adverse event as the following: "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." (FDA, 1995) The FDA further breaks down this category into serious and severe events. Severity of events are documented by intensity (e.g. mild, moderate, or severe), in contrast to seriousness of the event, which are coded by the patient outcome. (FDA, 1995)

In the academic allergy community, adverse drug reactions (ADRs) are defined by the Joint Task Force on Practice Parameters (which includes the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology) as any inadvertent drug reactions which are not intentional abuse or overdose, the result of an error in medication administration or "therapeutic failures". The incidence of ADRs is approximately 10% in hospitalized patients and 7% in outpatients. (Schnyder & Pichler, 2009).

Hypersensitivity events (HEs) are types of adverse drug reactions which are unpredictable and may not be dose related, however, these reactions are "characterized by objectively reproducible

symptoms and/or signs initiated by exposure to a drug at a dose tolerated by normal individuals". (Giavina-Bianchi, Patil, & Banerji, 2017) In addition, these reactions can be caused by immune mediated or non-immune mediated mechanisms. (Stone, Phillips, Wiese, Heddle, & Simon, 2014) Both types of HEs, immune and non-immune mediated, may be sudden and severe. (Stone, Phillips, Wiese, Heddle, & Simon, 2014), According to Gomes et al, drug hypersensitivity drug events comprise approximately a third of adverse drug reactions. (Gomes & Demoly, 2005)

Drug allergy an immune mediated hypersensitivity event, which is defined by the Joint Task Force as "an immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person." (Drug Allergy: An Updated Practice Parameter, 2010) A severe potentially life-threatening form of drug allergy is referred to as an anaphylactic reaction or anaphylaxis. This is in contrast to pseudo-allergic reactions, which are often referred to as "anaphylactoid reactions" and are not caused by IgE-mediated immune mechanisms. (Drug Allergy: An Updated Practice Parameter, 2010) In 2018, the World Allergy Organization recommended these types of reactions be referred to as "nonimmune anaphylaxis". It may seem contradictory to categorize these reactions in the "immune disorder" category in the adverse events tables, however, these reactions do involve immune related mechanisms such as mast cells (which release histamine) and basophils without an "immune complex formation" (antibody-antigen complex). (World Allergy Organization, 2018) Severe hypersensitivity reactions are commonly associated with cancer therapeutic agents such as monoclonal antibodies and chemotherapeutic agents as well as contrast agents. (World Allergy Organization, 2018) Figure 1 below displays the hierarchy of adverse drug events.

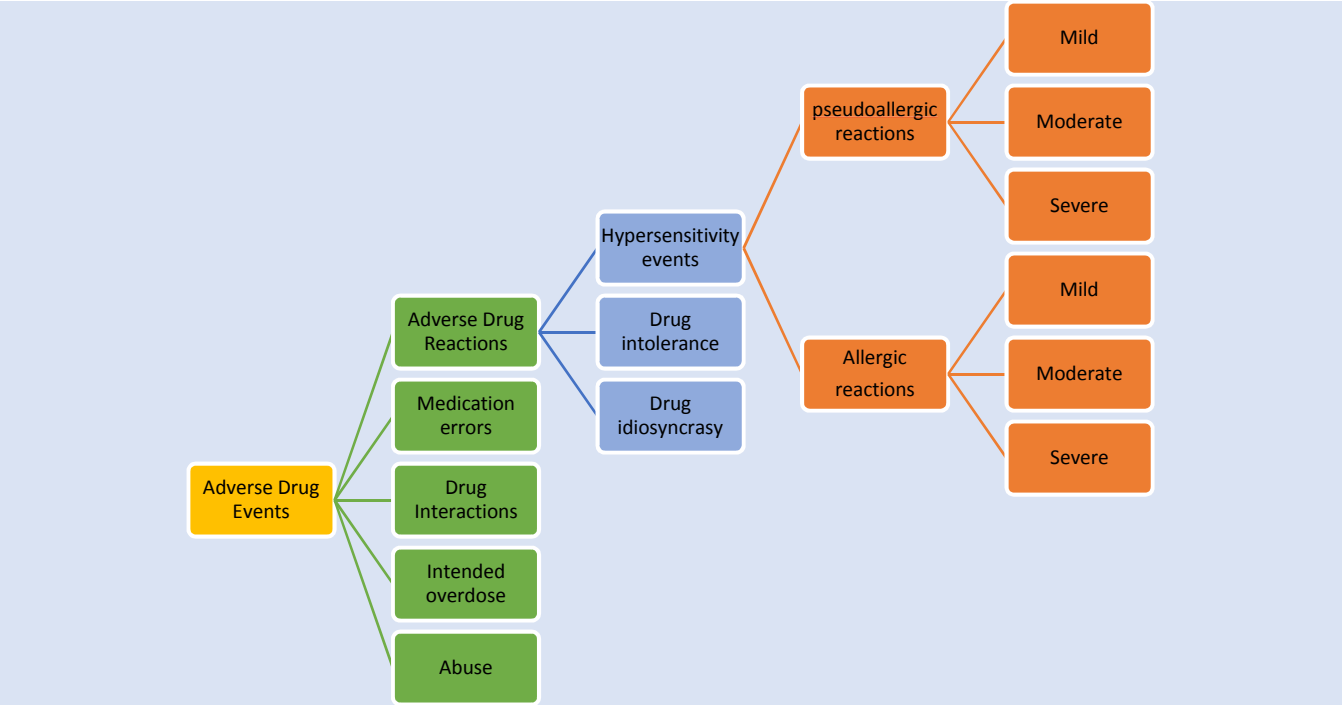
Anaphylactic type Reactions

The sudden and severe form of an allergic reaction is often referred to as anaphylaxis. (Stone, Phillips, Wiese, Heddle, & Simon, 2014) Although, this term had been previously poorly defined prior to 2010 and continues to be debated in some allergy circles. The definitions used to describe anaphylaxis include the words "serious" and "rapid onset" and often refer to the potential of shock and death as an outcomes. (American Academy of Allergy, Asthma & Immunology, 2020) (Simons, Ardusso, Bilo, Bilio, & et al., 2011). (National Cancer Institute, 2020) The World Allergy Organization guidelines published in 2011 lists the criteria for a "highly likely" diagnosis of anaphylaxis based on the timing of the onset of symptoms (sudden), the types of symptoms involved in the reaction, and whether or not the patient has been exposed to a "known allergen". (Simons, Ardusso, Bilo, Bilio, & et al., 2011) The generally accepted symptoms of this severe adverse event include: rash, wheezing, stridor, difficulty breathing, syncope, abdominal systems, and oral pharyngeal edema (swelling). (American Academy of Allergy, Asthma & Immunology, 2020) (Simons, Ardusso, Bilo, Bilio, & et al., 2011) The NCI Thesaurus definition also notes the physiology of the reaction in which histamine release occurs in response to allergen exposure. The term is listed as a lower level term (LLT) and as a disease or syndrome semantic type. (National Cancer Institute, 2020)

Anaphylaxis is increasing in incidence, currently thought to be approximately 4-50/100,000 person-years (Kim et al, 2014). Additionally, hospital admissions with a diagnosis of anaphylaxis have been increasing in number (Turner et al, 2015), which likely indicates increasing incidence of severe allergic reactions or could be due to improved reporting. Accuracy

and standardized reporting of HEs, especially immediate allergic, events in cancer clinical trials, allows for population level studies of the potential risk factors for these events. Population level studies, e.g. studies conducted using population-level healthcare databases, can improve the power of studies, especially in cases of rare forms of cancer or studies which may have low enrollment. Analysis of the potential risk factors involved in HEs aids in development of prevention and treatment protocols to improve patient safety. (Siverendran S, 2014)

Figure 1. Adverse Drug Reaction Types (FDA, 1995) (Vultaggio & Castells, 2014)



Hypersensitivity events in clinical cancer therapy

In addition to the increase in incidence of cancer in the population as discussed above, there is also a projected further increase in new cancer diagnoses of approximately 70% within the next twenty years. (Giavina-Bianchi, Patil, & Banerji, 2017) Several new therapies are developed each year. Therefore, the risk of hypersensitivity events during cancer treatment, with the use of chemotherapy and biological agents, will likely increase. In fact, a study of mortality data from the U.S. National Center for Health Statistics (NCHS) determined anti-neoplastic agents (cancer medications) as the third most common cause of fatal drug induced anaphylaxis. (Jerschow, Lin, Scaperotti, & McGinn, 2014)

Cancer Diagnostic and Therapeutic Agents

Cancer drugs and biological agents are commonly used in cancer treatment, and most of these drugs and agents have been associated with hypersensitivity events. (Lee, Gianos, & Klaustermeyer, 2009). Cancer therapy can be divided into several types of treatments which, according to the NCI, include the following: chemotherapy, immunotherapy, hormone therapy, radiation, targeted therapy, stem cell transplants, precision medicine and surgical treatments. This study will focus on chemotherapy (drug therapy) and immunotherapy (biological therapy). Immunotherapy can be used in precision medicine and target therapy. (NCI, 2015)

Several studies have noted the presence of hypersensitivity events to chemotherapy agents such as the platinum class of drugs which includes carboplatin. In the case of platinum agents, the adverse hypersensitivity events can be dose dependent, in contrast to taxanes and monoclonal antibodies which generally occur during the first or second infusion. (Lenz, 2007) Therefore,

research on predictors associated with the class of drug in an intervention can have a significant impact on the need for preparation and prevention of severe hypersensitivity events.

Biological therapies: Immunotherapy and targeted therapies

Biological agents differ from chemotherapy as these agents are derived from living organism or the substances are created in a laboratory to resemble the natural substances and used to eliminate cancer cells during therapy. (Dana-Farber Cancer Institute, 2017) According to the NCI, there are several types of biological therapies which are used to treat cancer, which are generally divided into the following categories by the NCI: Immune checkpoint inhibitors, immune cell therapy, therapeutic antibodies, therapeutic vaccines, and immune-modulating agents (NCI, 2018) Biological agents are associated with severe hypersensitivity infusion reactions and these reactions can be fatal.

Immunotherapy, which is a type of biological therapy, approaches the treatment of cancer from a different mechanism of action than chemotherapy. Immunotherapy works via either attacking the cancer cells or by mechanisms which stimulate the patient's own immune system to aid in targeting the cancer cells within the patient's body (NCI, 2018) (Dana-Farber Cancer Institute, 2017) Therapeutic antibodies are an example of a type of targeted cancer therapy, which are created in a laboratory to bind to cancer molecules to block the replication of cancer cells in the patient. (NCI, 2018)

Chemotherapy and Hypersensitivity Reactions

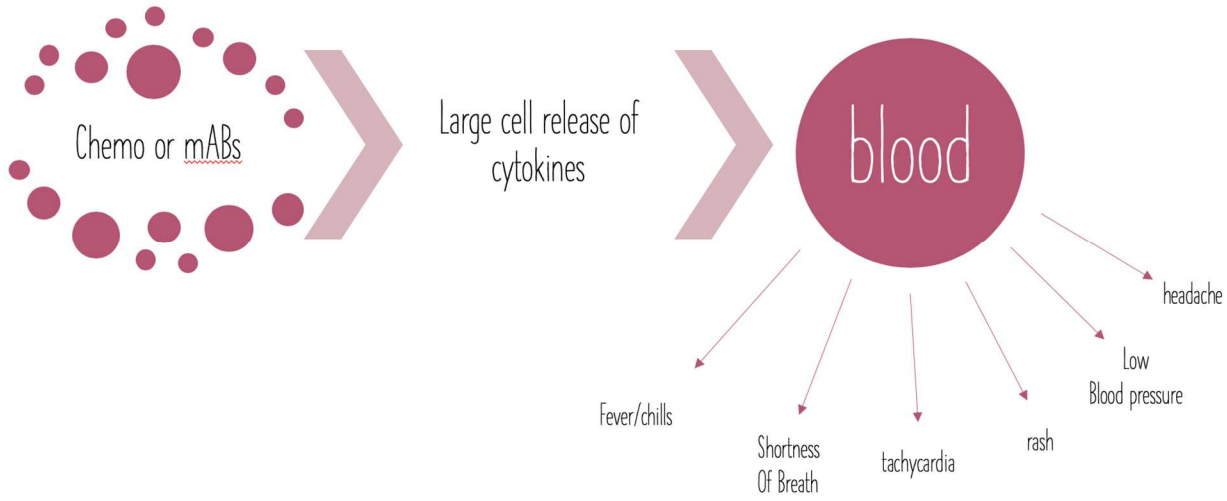
In contrast to biological therapies, chemotherapies have been the mainstay of cancer therapy for decades. These agents treat cancer by interfering with the cancer cell's ability to divide, therefore, inhibiting cancer growth. Unfortunately, these drugs have several adverse effects and can also affect the growth of normal cells, a common manifestation of this is hair loss. In addition, certain classes of chemotherapeutic drugs are frequently associated with adverse hypersenstivitiy events, and as noted above, some may correlated with the number of drug infusions. However, in certain drug classes, de-sensitization methods may be used prior to administration to the patient to minimize these adverse hypersenstivity events in at-risk patients. (Guitart, 2014) Therefore, using data-driven approaches to study clinical trial data can potentially aid in identifying the most likely etiologic agents and the patients at most risk of a life threatening response to drug administration.

Cytokine release syndrome

A severe adverse immune response associated with biological and chemical agents, e.g. monoclonal antibody (mAB) therapy, for cancer patients is cytokine release syndrome (CRS). This is an adverse immune event caused by the sudden release of immune substances referred to as "cytokines" from cells targeted and/or affected by the antibody therapy which result in several symptoms described in figure 2 below. However, the exact mechanism of how this occurs is not yet completely understood. (Shimabukuro-Vornhagen, et al., 2018) CRS may in some instances be referred to as an "infusion reaction" and can vary in severity from mild to severe (life threatening immune events). (Breslin, 2007) According to the NCI, most of these events are

mild to moderate in severity, however, some events can be life-threatening. (National Cancer Institute, n.d.)

Figure 2. Etiology and Symptoms of Cytokine Release Syndrome



An important point to highlight here is the similarities in terminology descriptive needs between CRS and anaphylactic events. Both events may vary in severity and have been associated directly with specific allergens. Additionally, both events have several symptoms which may be recorded separately and not specifically as the syndrome itself, e.g. chills or wheezing.

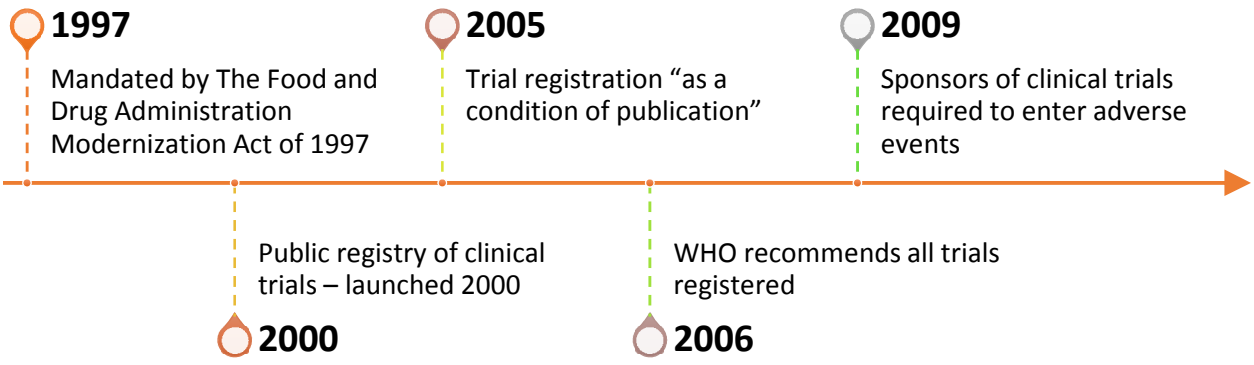
Brief History of ClinicalTrials.gov

The Food and Drug Administration Modernization Act of 1997 (FDAMA) included a section requiring the National Institute of Health to create a public registry of clinical trials, specifically trials which involved drugs treating life-threatening health conditions (U.S. National LIbrary of Medicine ClinicalTrials.gov, 2018). The legislation is intended to improve public access to

health information on clinical trials of experimental therapies. In 2000, the ClinicalTrials.gov website was launched. (Press Release: National Institutes of Helath Launches "ClinicalTrials.gov", 2000) In 2005, further legislation was published by the International committee of Medial Journal Editors to require trial registration “as a condition of publication”. (ClinicalTrials.gov, 2018) The following year, the World Health Organization (WHO) recommended that all clinical trials be registered. WHO created their own platform, which incorporates data from ClinicalTrials.gov. (World Health Organization, 2019)

In 2007, Public Law 110-85 Sec. 801, “Expanded Clinical Trial Registry Data Bank”, was passed by Congress requiring expansion of the current data entry requirements for this clinical trial registry and public online access. Required reporting included: clinical trial title, summary, study type and design, primary and secondary outcomes, demographic data, dates. (Congress, 2007) In 2009, sponsors of clinical trials were required to enter adverse event reports into ClinicalTrials.gov. (Neuer, 2009)

Figure 3. Timeline of ClinicalTrials.gov Milestones



Cancer Adverse Event Reporting in ClinicalTrails.gov

Clinicaltrials.gov uses the following definition for adverse events:

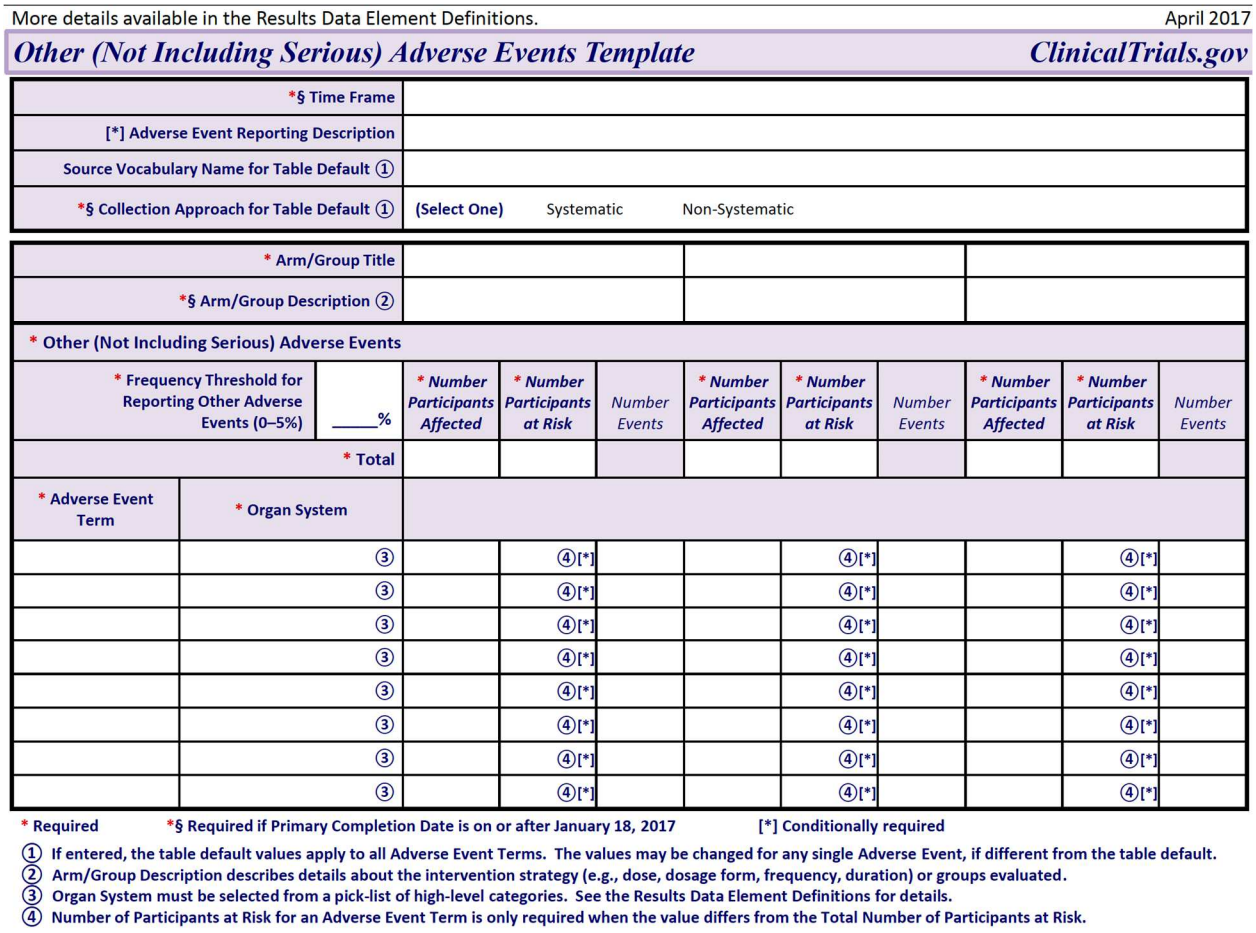
> Any untoward or unfavorable medical occurrence in a participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research. (ClinicalTrials.gov, 2018)

Adverse event types recorded in Clinicaltrails.gov are entered into the following three adverse event tables by the clinical trial investigator: All-cause mortality; Serious adverse events (AEs); Other (Not Including Serious) AE . (ClinicalTrials.gov, 2018)

In clinicaltrials.gov, adverse event reporting is not required to follow a specific standard terminology or classification system. Rather, adverse event data is entered into the three tables using the investigators standard vocabulary or classification system of choice. However, there is a requirement for investigators to enter adverse event reporting into semi-structured tables which follow an organ system category approach used by the Medication Dictionary for Regulatory Activities (MedDRA). (Goss, et al., 2013)

Adverse event data elements include the following: Time frame, description, source vocabulary name, collection approach (systematic vs. non-systematic), total number affected, total number at risk, and organ system. Investigators submit this data into semi-structured "Serious Adverse Event" and "Other (Not Including Serious)" tables organized by organ systems. Please see the example screen shot in Figure 4 below of an "Other (Not Including Serious)" adverse event result table.

Figure 4. Screenshot of Other (Not Including Serious) Adverse Events Table



More details available in the Results Data Element Definitions. April 2017

Other (Not Including Serious) Adverse Events Template *ClinicalTrials.gov*

*§ Time Frame	
[*] Adverse Event Reporting Description	
Source Vocabulary Name for Table Default ①	
*§ Collection Approach for Table Default ①	(Select One) Systematic Non-Systematic

* Arm/Group Title										
*§ Arm/Group Description ②										
* Other (Not Including Serious) Adverse Events										
* Frequency Threshold for Reporting Other Adverse Events (0–5%)	_____%	* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events
* Total										
* Adverse Event Term	* Organ System									
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
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	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① If entered, the table default values apply to all Adverse Event Terms. The values may be changed for any single Adverse Event, if different from the table default.
② Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
③ Organ System must be selected from a pick-list of high-level categories. See the Results Data Element Definitions for details.
④ Number of Participants at Risk for an Adverse Event Term is only required when the value differs from the Total Number of Participants at Risk.

(U.S. National Library of Medicine, 2017)

ClinicalTrails.gov data element definitions are listed on their website and can be retrieved at: https://prsinfo.clinicaltrials.gov/results_definitions.html#AdverseEvents

Currently, the National Library of Medicine has begun an effort to "modernize" this website and database in order to improve its usability for investigators, patients, family members and researchers who use this data for secondary population level research. (U.S. National LIbrary of Medicine, 2020) This project will also provide necessary feedback to support this project.

Medical Terminologies for Adverse Drug Reporting

In the 1990's, the need for more standardized reporting of clinical trial outcomes and adverse events was evident to researchers and journal editors who responded to this need with the Consolidated Standards of Reporting Trials (CONSORT) statement. (Peron J, 2012) The specialized need for improvement in the comprehensiveness and quality of reporting of adverse events and outcomes in randomized controlled trials, especially in cancer clinical trials where potential drug toxicities and narrow therapeutic indexes are common, was apparent. (Ghimire S, 2014)

To address this gap in standardized clinical trial reporting, the National Cancer Institute developed a controlled classification system specifically to record adverse events in clinical cancer trials called Common Toxicity Criteria (CTC) created in 1983, and updated with a version 2 prior to the change in name. (Trotti, et al., 2003) In 2006, the Common Terminology for Adverse Events or CTCAE version 3.0 was published, CTC was rename CTCAE removing "toxicity" from its name. (Trotti, et al., 2003) This terminology is organized according to the MedDRA system organ class. Adverse events each have a specific definition and the events are graded based on severity criteria. The latest version for cancer adverse reactions mapping (version 5) is current available on the National Cancer Institute website (NCI). According to the CTCAE quick reference guide, CTCAE version 5 not only uses the same system organ classification as MedDRA, this version has also incorporated elements of MedDRA's terminology. (U.S. Department of Health and Human Services, 2017)

Common Terminology Criteria for Adverse Events in Cancer Clinical Trials

The Common Terminology Criteria for Adverse Events (CTCAE) was developed by the National Cancer Institute to record common adverse events in clinical cancer trials. The use of this classification system is required for recording adverse events in any NCI funded clinical cancer research study. The CTCAE classification system consists of twenty-eight categories of adverse events groups by MedDRA's System Organ Class (SOC). Each of these SOC, include relative adverse events to the SOC and each adverse event uses grading scales based on clinical criteria which include symptoms, signs, vitals and laboratory to classify severity. (National Cancer Institute, 2020) (Richesson, Fung, & Krischer, 2008) The general guideline for grade levels of severity in CTCAE is shown in Figure 3 below, however, the criteria to meet each level is specific for the adverse event shown using anaphylaxis as an example in Table 2 below. In order for an event to be included in a severity level, the clinical trial participant experiencing the event should exhibit one or more of the criteria included in that grade. Therefore, it is difficult to assess which of these criteria were present and which criteria were not present in the particular grade level to classify the adverse event in grades 1-5. When performing large population level studies using big data from sites such as ClinicalTrials.gov, investigators are unable to determine the sign or symptom specifically, only the severity grade. If evidence-based medicine and clinical research in subsequent versions of CTCAE lead to updates in the criteria necessary meet the standard for the severity level for a particular disease or condition, the ability to aggregate grade levels could be affected and the inclusion of the events from prior years in longitudinal studies would require some level of mapping between the versions. (Richesson, Fung, &

Krischer, 2008) Therefore, improving the granularity of the terms would improve data aggregate quality.

Prior to the development of CTCAE, the NCI used the Common Toxicity Criteria (CTC) which was developed in 1994 with version one and last updated in 2017 with version five. (EORTC, n.d.) The two types of classification systems overlapped in use for some time, however, CTCAE is currently more the preferred classification system used by the NCI. Both classification systems are listed under the Cancer Therapy Evaluation Program, however, CTC has been archived. (National Cancer Institute, 2020)

Table 1. CTCAE Grading Scale for Severity of Adverse Events

Grade	Severity Level	Description
1	Mild	Asymptomatic or mild symptoms, no intervention
2	Moderate	Minimal or non-invasive intervention indicated; limits instrumental ADLs
3	Severe	Severe but not immediately life-threatening; hospitalization: limiting self-care ADLs
4	Life-threatening	Urgent intervention indicated
5	Death	Death related to AE

Reference: Adapted from "Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (U.S. Department of Health and Human Services, 2008)

Unfortunately, a cancer trial study using data from the years 2012-2013 revealed that categories used to encode AEs and grade levels were often incorrectly coded. (Zhang, Liang, & Tannock,

Use and misuse of common terminology criteria for adverse events in cancer clinical trials, 2016) (Zhang, Chen, & Wang, The use of and adherence to CTCAE v3.0 in cancer clinical trial publications, 2016) Currently, CTCAE version 5 is available for download at the NIH National Cancer Institute website. (National Cancer Institute, 2018) To our knowledge, no further study of later CTCAE versions has been published.

CTCAE, in contrast to MedDRA, possesses the ability to code an "allergic reaction" at all five grades, however, there is no ability to code "anaphylaxis" at the lower severity grading levels (one and two) due to the severity of this particular condition. In CTCAE and SNOMEDCT_US, the preferred term (PT) is "Anaphylaxis", in comparison to MedDRA in which the PT is "Anaphylactic reaction". (National Cancer Institute, n.d.) Other synonyms to this term are acute anaphylaxis, acute anaphylactic reaction, generalized anaphylaxis, systemic anaphylactic reaction, and systemic anaphylaxis. The term "anaphylactic shock" is also used which indicates signs and symptoms of shock, such as decreased blood flow, loss of consciousness and/or hypoxia, were present as one or more of the symptoms. (National Cancer Institute, n.d.) Please see Table 2 below which describes the NCI terms and their corresponding grades.

Table 2. CTCAE Severity Scale for HE allergic type (U.S. Department of Health and Human Services, 2017)

NCI CTCAE v5.0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic Reaction*, CTCAE (C143271)	C143969 Systemic intervention not indicated	C144506 Oral intervention Indicated	C145125 Bronchospasm; Hospitalization indicated for clinical sequelae; Intravenous intervention indicated	C145738 Life-threatening consequences; urgent intervention indicated	C146208 Death
Anaphylaxis*, CTCAE (C1 43282)	n/a	n/a	C145135 Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	C145744 Life-threatening consequences; urgent intervention indicated	C146214 Death
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death

***** If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.

Reference: Adaptive from the NCI CTEP Cancer Therapy Evaluation Program CTCAE v5.0 Quick Reference 5 x 7. (U.S. Department of Health and Human Services, 2017)

MedDRA and its relationship to CTCAE

According the National Cancer Institute website's NCI Term Browser, CTCAE is "harmonized with MedDRA at the Adverse Event (AE) level." (National Cancer Institute, 2020) CTCAE draws from the high-level terms used by MedDRA's System Organ Class (SOC) hierarchy as it uses the same body system level classification of adverse events, e.g. immune system disorders is the category used to classify hypersensitivity events. In contrast, MedDRA does not assign each adverse event term a grade level based on severity. (U.S. Department of Health and Human Services, November) Mappings of each version of CTC or CTCAE to MedDRA are available on the NCI website. (National Cancer Institute, 2018)

Lack of consistent use of controlled terminology

"Large data sets are hindered by lack of robust utilised coding systems, with underreporting, miscoding and many cases of "unspecified" triggers in admissions and fatality registers" (Turner & Campbell, 2017) Lack of standards in the terms used to describe anaphylaxis and collection methods remains a challenge to studying this type of severe adverse event on a population level in large databases, however, this type of study has not been conducted in clinical trial data to our knowledge. (Turner & Campbell, 2017) Effective use of terminologies and/or classification systems to represent anaphylactic and anaphylactoid events could begin to address this challenge, however, to compound the problem, Clinicaltrials.gov allows for any type of standard terminology or classification system to allow for investigator flexibility when entering the adverse events into the three AE summary tables: All-Cause Mortality, Serious Adverse Events and Other (Not including Serious) Adverse Events. Additionally, there is no requirement to specify which type of terminology or classification system was used. (ClinicalTrials.gov, 2018)

Variation in Adverse Event Clinical Trial Collection Methods

Time frame, AE description, source vocabulary, and collection approach are also recorded by the investigator. Again, investigators are not mandated to use a particular type of adverse event collection method or terminology/classification system, rather, they are instructed to add the information on the method and system into the adverse event table and this is latter added as a footnote after each term (see figure 5 below in Chapter 3. Methods). The permissable values for collection methods reported may be either systematic assessment, non-systematic assessment or not specified. Systematic assessment as a data collection is defined by ClinicalTrials.gov as a consistent method (e.g. protocol, questionnaire, diary, etc.) of routinely assessing clinical trial participants for adverse events either during visits or using reporting tools, in contrast to their definition of a non-systematic assessment method which relies primarily on patient self-reporting and "unsolicited" with no formal methods or protocol of collecting adverse events. (ClinicalTrials.gov, 2018) (U.S. National Library of Medicine, 2017)

Challenges in allergy documentation in EHRs as noted by Goss et al in their study of the comprehensiveness of standard terminologies to capture allergy, a type of hypersensitivity reaction. Only SNOMED CT was able to document lack of allergies (e.g. NKDA) as of the 2013 article publication date. Additionally, the authors found RxNorm better for drug related allergies and UNII for food and substance allergens. The investigators note MedDRA "lacks formal definitions to relate manifestation to causative agent or severity" and "excludes information on drug/product terminology" which explains why the use of the RxNorm terminology system maybe a better choice in the case of drug hypersensitivity events. (Goss, et al., 2013) This is concerning given that MedDRA is one of the most common terminology types used in

ClinicalTrials.gov and the basis for the categorization of the adverse event tables. Perhaps, this is due to the easy of entering the data into the same organ system categories.

Previous Work on Evaluation of the Comprehensiveness of Terminologies in Hypersensitivity Reporting of allergic events

Goss et al. evaluated the encoding of allergy by comparing SNOMED CT, NDF-RT, RxNorm, UNII, and MedDRA. The group analyzed each of these controlled terminologies and how they compared to each other with regards to their content coverage and ability to encode both the reaction and the etiologic agent when encoding allergy events in electronic health records. SNOMED CT was found to be the most comprehensive standard terminology (also uses post-coordination), however, RxNorm was noted to be a good method to encode drug allergens. The authors state the challenges unique to encoding allergic reactions which include the need to code the etiologic allergen, the symptoms/signs, the severity of the event and the addition of negative findings (e.g. no known drug allergies or no known allergies). (Goss, et al., 2013)

Furthermore, different versions of the same controlled terminology or classification system can drastically change the ability of the terminology or system to capture adverse events. For example, a study of the incidence of adverse events in Bevacizumab therapy in patients being treated for glioma using different versions of CTCAE (3.0 & 4.0) noted a large difference in the incidence of severe hypertensive events. CTCAE version 3.0 reported 9.5% vs. 45.2% in version 4.0. (Bumes, et al., 2016) This is likely due to a change in criteria to meet the severe level of this category.

CHAPTER THREE: METHODS

Part 1: Creating the original dataset of hypersensitivity adverse events in cancer clinical trials

Data Source

The data used in this study was obtained from ClinicalTrials.gov (discussed above). Semi-structured adverse event tables are available for secondary study of clinical trial data. The data used was collected from September 20, 1999 to March 2018.

The full dataset from clinicaltrial.gov was obtained in March 2018. After retrieving 255,065 datasets, filters were used to find clinical trials with recorded hypersensitivity events.

Please see below for the set of filters:

```
allTrials = get_trials_from_source('clinicaltrial.gov')    # get all clinical trials
from the website
filter.filter_trials_by_valid_clinical_results(allTrials)   # only selecting clinical
trials with valid adverse event/Other event results
filter.filter_by_category(categoryName = 'Immune system disorders') # only
select the section named "immune system disorders" in adverse event reports
filter.filter_by_drug_list(drugList= drugSource.DrugList) # only select trials that
use at least one of drugs in specified drug list"
filter.filter_by_condition(conditionName = cancer_terms)  # the overall report
must contain at least one cancer terms from the cancer-terms list
```

Original dataset was created using NLP methods. An XML parser was created to extract readable text data from adverse event tables from ClinicalTrails.gov.

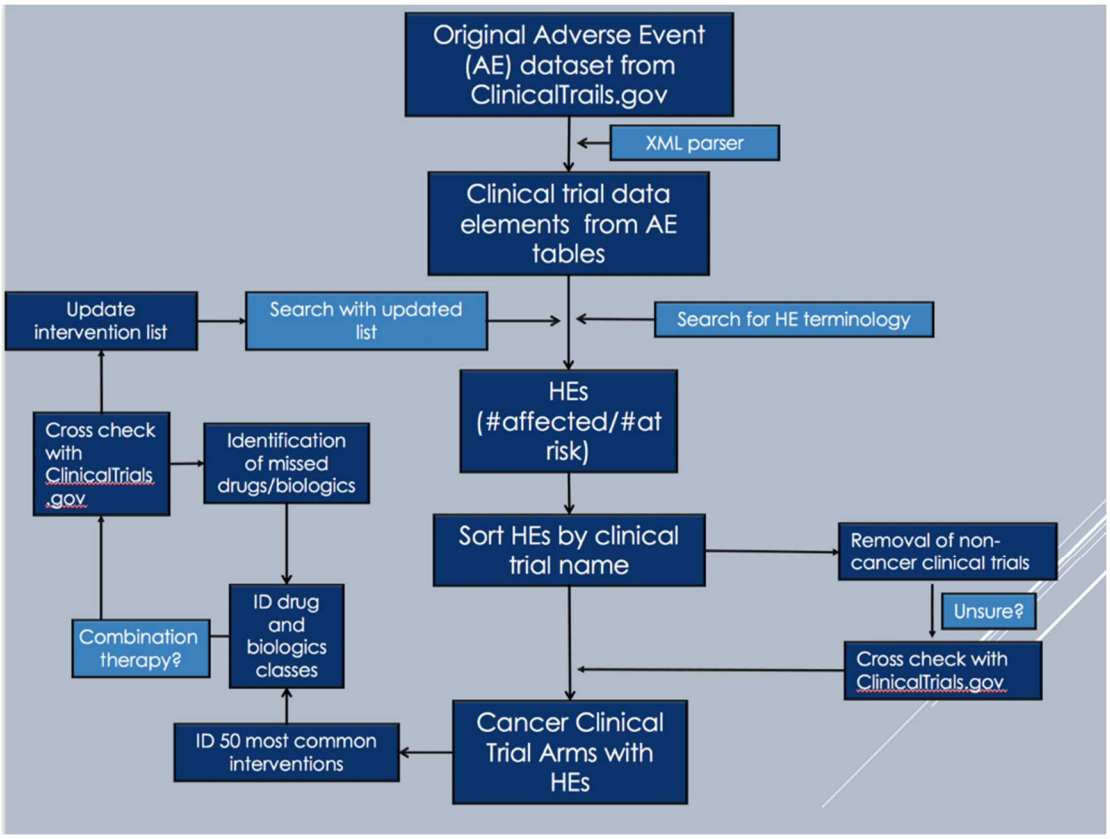
Steps to create the drug and biological intervention terms list

1. An initial query of the data from ClinicalTrials.gov was queried was performed in 2016 to extract HEs using the following terms: Hypersensitivity, allergic reaction, allergy, anaphylaxis, dermatitis allergic, drug hypersensitivity and infusion reaction. After the results were reviewed, the query was expanded to include broader category of "immune disorder". A cancer intervention drug list was created from the clinical trial intervention variable using a data driven approach. (see Figure 2 below)
2. Frequency analysis of the intervention words in the clinical trial intervention section was performed to identify the most commonly used intervention words using for describing drug interventions
3. Words were analyzed manually and incomplete or non-intervention words were removed. (e.g. "Na+" or "and"). The list of removed terms was archived as a reference baseline.
4. An Oncology Fellow reviewed and removed non-chemotherapy agents or chemotherapy agents that are not currently used in cancer therapy
5. Duplicate interventions were removed.
6. Cancer drugs were classified by drug class in consultation with the Oncology Fellow

7. Cancer trial interventions were then split into two broad groups: Single therapies and Combination drug therapies.
8. Another query for hypersensitivity reactions was performed using a join with this newly created common cancer drug intervention term list to search the original database of clinical trial adverse reactions (#1) again (iterative process).

See Appendix A for complete list of drugs and biological agents.

Figure 5. Original data pipeline



Part 1a: Data Quality Analysis

1. Data was analyzed for spelling errors and use of abbreviations. This were corrected.

2. NCI trial arms were reviewed while recording terminology types manually, randomly selected clinical trials were verified by returning to the original data in ClinicalTrials.gov to test for accuracy of numbers of affected and at risk clinical trial participants.
3. NLP data extraction errors were returned to the lab for analysis and correction of the data pipeline and NLP methods.
4. After data corrections, random records were again selected for a final data quality check.

Part 2: Descriptive analysis of the dataset and creation of a subset of severe events

The dataset was analyzed descriptively to provide a population level view of the characteristics of immune disorder hypersensitivity events in cancer clinical trials: Cancer types, drug interventions, number of participants affected, number of participants at risk, number of serious events and number of other (not including serious events).

Additionally, severe anaphylactic, anaphylactoid and grade 3-5 hypersensitivity adverse events were identified as a subset of the original dataset. This subset of severe events was analyzed using pivot tables in Excel. A pivot table of the data points "adverse event" and "sum of affected number" and "sum of at-risk number" in each clinical trial arm was created. Furthermore, another pivot table was created with the severe anaphylactic type events along with the severity level for each event, number of clinical trial arms, number of affected participants and number of at-risk participants. CRS events were not included in this subset as it was not possible to determine if the events were severe due to the lack of grading of these events.

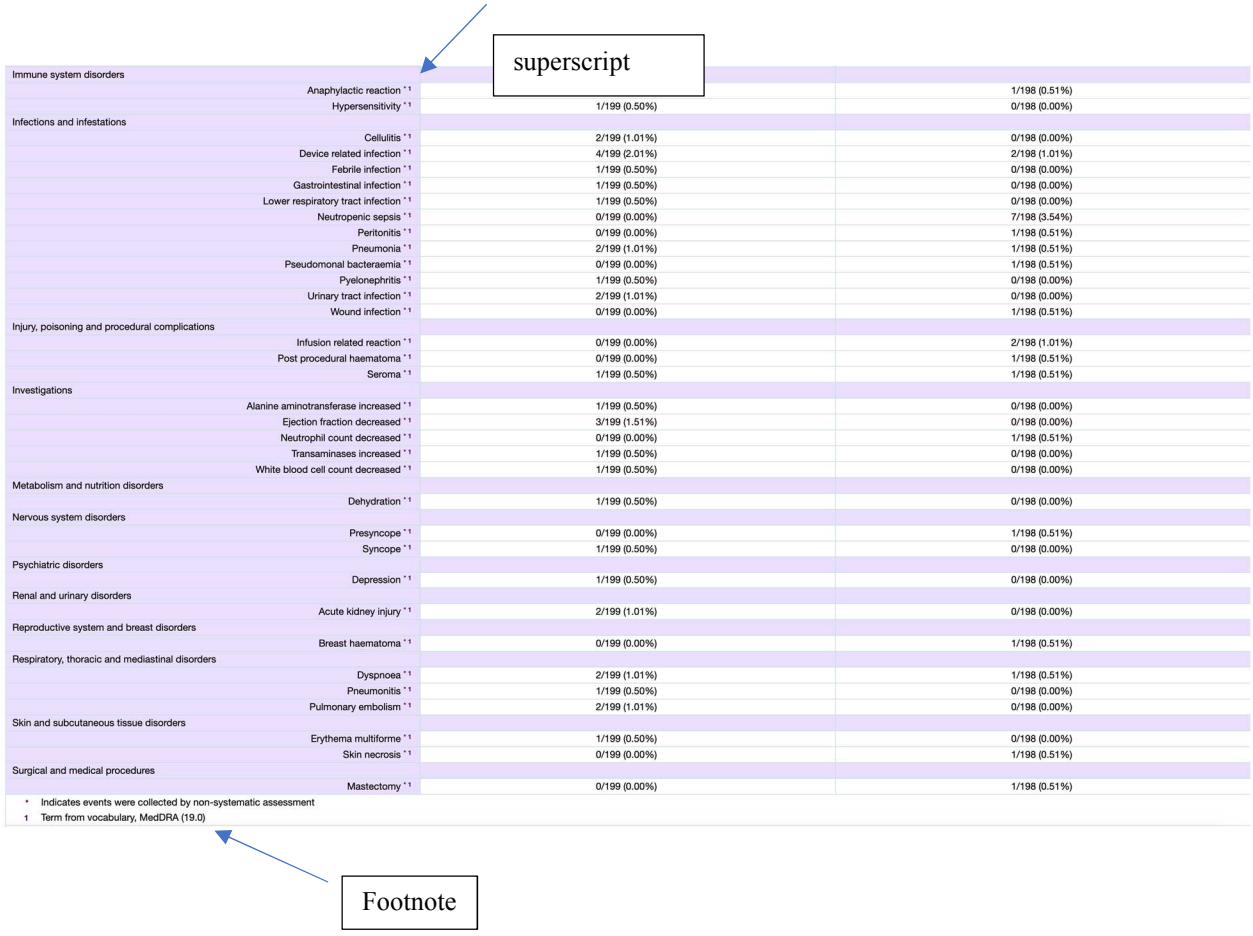
Part 3. Terminology evaluation

The subset of severe anaphylactic and anaphylactoid type adverse events was analyzed to determine the type of controlled terminology or classification system used to record each of these adverse events. Unfortunately, this data point was not discretely recorded in the adverse event tables within ClinicalTrials.gov. Instead, the terminology or classification system for each clinical trial was reported as a footnote at the bottom of each adverse event table, the table for serious events and the table for other (not including serious) events. Please see the screenshot below in Figure 6 below. Therefore, manual data extraction of these data points was required.

The two data points, controlled terminology/classification system and adverse event data collection methods, were entered into two newly created columned in the Excel spreadsheet for analysis. In addition, the date of the first result entry and the date of last result update for each clinical trial arm was recorded in two more discrete data columns within the spreadsheet. Pivot tables were created to analyze clinical trial investigator choice of controlled terminology/classification system for each term which representing a severe hypersensitivity adverse event. Then, descriptive analysis was performed to determine the total number of different terminology and classification system types used to describe these events. Also, the total number of clinical trial participant adverse events and the total number of at-risk clinical trial participants was determined for each adverse event term and terminology/classification system in the severe hypersensitivity data subset.

In cases where there were no superscript or footnotes, the clinical terminology and collection method was recorded as “not specified”. Using the date of first recorded result, tables of terminology/classification systems by initial year of use and date ranges of terminology/classification system use was created. Additionally, the number and types of versions of each system was determined.

Figure 6. Screen Shot of Clinical Trial Adverse Event Results with Controlled Terminology Type and Collection Method



Immune system disorders		
Anaphylactic reaction [*1]		1/198 (0.51%)
Hypersensitivity [*1]	1/199 (0.50%)	0/198 (0.00%)
Infections and infestations		
Cellulitis [*1]	2/199 (1.01%)	0/198 (0.00%)
Device related infection [*1]	4/199 (2.01%)	2/198 (1.01%)
Febrile infection [*1]	1/199 (0.50%)	0/198 (0.00%)
Gastrointestinal infection [*1]	1/199 (0.50%)	0/198 (0.00%)
Lower respiratory tract infection [*1]	1/199 (0.50%)	0/198 (0.00%)
Neutropenic sepsis [*1]	0/199 (0.00%)	7/198 (3.54%)
Peritonitis [*1]	0/199 (0.00%)	1/198 (0.51%)
Pneumonia [*1]	2/199 (1.01%)	1/198 (0.51%)
Pseudomonal bacteraemia [*1]	0/199 (0.00%)	1/198 (0.51%)
Pyelonephritis [*1]	1/199 (0.50%)	0/198 (0.00%)
Urinary tract infection [*1]	2/199 (1.01%)	0/198 (0.00%)
Wound infection [*1]	0/199 (0.00%)	1/198 (0.51%)
Injury, poisoning and procedural complications		
Infusion related reaction [*1]	0/199 (0.00%)	2/198 (1.01%)
Post procedural haematoma [*1]	0/199 (0.00%)	1/198 (0.51%)
Seroma [*1]	1/199 (0.50%)	1/198 (0.51%)
Investigations		
Alanine aminotransferase increased [*1]	1/199 (0.50%)	0/198 (0.00%)
Ejection fraction decreased [*1]	3/199 (1.51%)	0/198 (0.00%)
Neutrophil count decreased [*1]	0/199 (0.00%)	1/198 (0.51%)
Transaminases increased [*1]	1/199 (0.50%)	0/198 (0.00%)
White blood cell count decreased [*1]	1/199 (0.50%)	0/198 (0.00%)
Metabolism and nutrition disorders		
Dehydration [*1]	1/199 (0.50%)	0/198 (0.00%)
Nervous system disorders		
Presyncope [*1]	0/199 (0.00%)	1/198 (0.51%)
Syncope [*1]	1/199 (0.50%)	0/198 (0.00%)
Psychiatric disorders		
Depression [*1]	1/199 (0.50%)	0/198 (0.00%)
Renal and urinary disorders		
Acute kidney injury [*1]	2/199 (1.01%)	0/198 (0.00%)
Reproductive system and breast disorders		
Breast haematoma [*1]	0/199 (0.00%)	1/198 (0.51%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea [*1]	2/199 (1.01%)	1/198 (0.51%)
Pneumonitis [*1]	1/199 (0.50%)	0/198 (0.00%)
Pulmonary embolism [*1]	2/199 (1.01%)	0/198 (0.00%)
Skin and subcutaneous tissue disorders		
Erythema multiforme [*1]	1/199 (0.50%)	0/198 (0.00%)
Skin necrosis [*1]	0/199 (0.00%)	1/198 (0.51%)
Surgical and medical procedures		
Mastectomy [*1]	0/199 (0.00%)	1/198 (0.51%)

* Indicates events were collected by non-systematic assessment
1 Term from vocabulary, MedDRA (19.0)

Part 4: Methods used to test each hypothesis

Hypothesis #1:

The ability to accurately document severity of hypersensitivity events secondary to cancer biological or chemotherapy agents is improving with the use of the CTCAE classification system and its emphasis on severity levels in comparison to MedDRA.

Test of presence of severity grade

To test the hypothesis that the CTCAE classification system has improved the ability of clinical investigators to capture the severity of severe anaphylactic and anaphylactoid events in clinical cancer trials in comparison to MedDRA, first the terms used to describe these events in both systems were analyzed and categorized in to groups based on the type of terminology used to describe the event and whether a grade level was included, for example CTCAE terms with a grade, CTCAE with no grade, MedDRA terms with a grade, MedDRA terms with no grade, terms with no specified terminology with a grade etc. MedDRA is expected to not include grade levels, therefore, CTCAE should in theory, perform better in capturing hypersensitivity event severity. Second, due to low cell levels of less than 5, a Fisher's exact test was used to test the statistical difference between categories. The category of cytokine release syndrome/infusion reaction events was analyzed separately as these are categorized differently in CTCAE as discussed in Chapter 2.

Test of accuracy of hypersensitivity adverse event severity

The data subset of severe anaphylactic and anaphylactoid adverse events was categorized into two subgroups: Serious events and other (not including serious) events. Anaphylactic and anaphylactoid types events are by definition severe and as discussed in Chapter 2, the classification system for CTCAE does not allow for coding of these events at grades lower than three (severe). Therefore, adverse events reported by clinical trial investigators as "other (not including serious)" have not accurately recorded the severity level of the anaphylactic or anaphylactoid adverse event.

To test the hypothesis of whether the NCI CTCAE classification system with its emphasis on severity grade levels (one through five) is improving the ability to accurately record hypersensitivity event severity, the most common terms from the severe data subset were divided into four subgroups: anaphylactic events labeled serious using the MedDRA term "anaphylactic reaction"; anaphylactic events mislabeled as other using the MedDRA term "anaphylactic reaction"; anaphylactic events labeled serious using the CTCAE term "anaphylaxis" or "anaphylaxis to X" or "X anaphylaxis" where X is equivalent to the antigen; and anaphylactic events mislabeled other using the CTCAE term "anaphylaxis". Given both terms represent severe events, neither term should be represented in the "other (not including serious)" adverse event table. In other works, the value for adverse hypersensitivity events labeled with one of these two terms should be labeled as serious and not labeled as other than serious as discussed in Chapter 2. Please see Table 4 below.

Table 3. Method for comparing accuracy of severity label for severe hypersensitivity events

Term	Serious Events	Other Events	Total
Anaphylactic Reaction (MedDRA Term)	A	B	A + B
Anaphylaxis (CTCAE Term)	C	D	C + D
Total	A + C	B + D	A + B + C + D

The percentage of severe events coded as "other (not including serious) was determined for each term. Additionally, the statistically difference between the observed events in each category was compared to the expected events in each category. The expected number in each category was determined by multiplying the total number of events in the corresponding column by the corresponding row and dividing the product by the total number of events. For example, in Table 3, the expected number of serious anaphylactic events mislabeled as "other than serious" using the MedDRA term "anaphylactic reaction" was determined by (B+D)*(A+B)/(A+B+C+D). A Chi Square test was then used to determine if there was a significant difference between the MedDRA terms, CTC terms, CTCAE terms, and Not Specified terms groups. (Hall & Richardson, 2016)

Hypothesis #2:

Terms used to describe severe anaphylactic and anaphylactoid events recorded in the dataset of clinical cancer trials from ClinicalTrials.gov rarely (<5% of events) include the antigen responsible for the event which hinders the ability to study incidence of drug and biological agent induced hypersensitivity events when the clinical trial intervention includes multiple drugs

and/or multiple therapeutic agents. In other words, there is no statistical difference between the types of terminologies or classification systems used regarding the inclusion of the antigen within the severe hypersensitivity event term.

The subset of severe anaphylactic and anaphylactoid adverse events which included the terms anaphylaxis, anaphylactic reaction, anaphylactic shock, and grade 3 or 4 allergic or hypersensitivity reactions, and variations of these terms, e.g. "Bactrim anaphylaxis", were categorized into groups by the type of controlled vocabulary or classification system and whether the term including the name of the allergen which was the etiology of the severe hypersensitivity event. The categories were compared statistically with the Fisher's exact test (due to cell numbers less than 5) to determine if a statistical significance exists between the terminology, classification system, or unspecified terminology groups with regards to the inclusion of the allergen. The same method was used to analyze the cytokine release syndrome and infusion reaction group.

Hypothesis #3: *Over 25% of the severe anaphylactic and anaphylactoid events have <u>not</u> been collected using a systematic assessment method which could result in underreporting of events.*

Data regarding collection approach methods were reported as a footnote below the semi-structured adverse event tables in ClinicalTrials.gov which required manual data extraction of the descriptive terminology and data collection method. Please refer to Figure 5 above. The unique NCI identification number of the trial arm was used to query the database via the search engine found at the ClinicalTrial.gov home page. Adverse event collection methods were

recorded in a separate column in the datasheet as either systematic assessment, non-systematic assessment or unspecified collection method which are the only permissible values in the adverse event tables, see Figure 4 above. The incidence of use of a systematic assessment collection method was calculated for severe hypersensitivity adverse events using the most commonly recorded terms: anaphylaxis, anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction. Each adverse event was categorized by term and collection method. A Chi Square test was used to analyze if there was a significant difference between the terms used and the collection method.

Chapter IV. Results

Descriptive Analysis

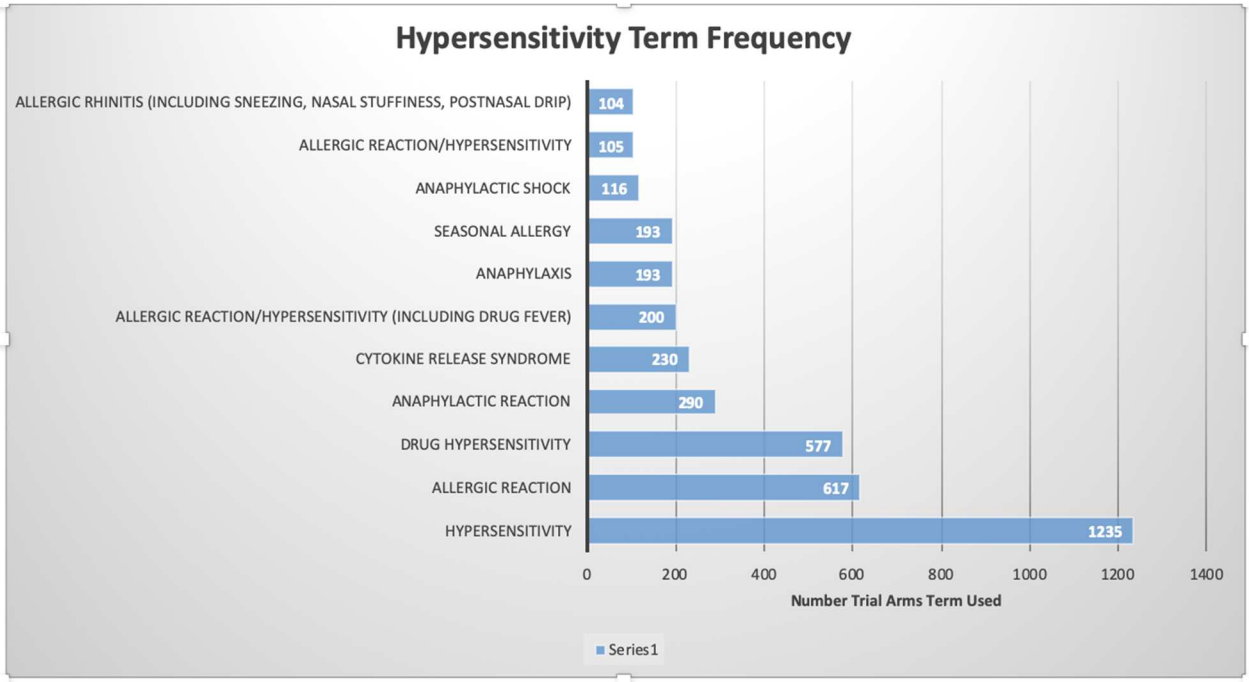
The final dataset of adverse immune events included 1331 NCT unique clinical trial ID numbers and 5595 clinical trials arms (each clinical trial may have more than one). The results of the descriptive analysis of total immune system disorder events, in all clinical trials reporting adverse events, returned 13,088 recorded adverse immune mediated events out of 895,383 participants at risk for an event after exposure to a clinical trial arm intervention. These results indicate an overall incidence of 0.0146 or approximately 1.5% for adverse immune related events in this clinical cancer trial dataset over the timeframe of September 1999-March 2018.

These 1331 clinical cancer trials involved 639 unique cancer condition combinations. Some of the cancer conditions were included in more than one trial. For example, one trial investigated interventions for B-cell lymphoma and follicular lymphoma while another trial investigated B-cell lymphoma in addition to several other types of lymphoma such a T-cell lymphoma. The most commonly reported types of cancer in the clinical trials reporting immune disorder events were breast cancer/neoplasms, multiple myeloma, colorectal cancer, lymphoma, leukemia and non-small cell lung cancer. Some conditions were labeled only as “cancer”, “neoplasms”, “solid tumor” or “carcinoma” which made analyzing the cancer type difficult.

The most frequently used term to describe immune disorder adverse events in clinical trial arms was “hypersensitivity”. This high-level term was used in approximately 22.1% of clinical trial arms, nearly one quarter. It also has the least ability to provide detail on allergen and severity. The next most frequently used terms to describe these events were: allergic reaction (11.0%),

drug hypersensitivity (10.3%), anaphylactic reaction (5.2%), cytokine release syndrome (4.1%), allergic reaction/hypersensitivity (including drug fever) (3.6%), anaphylaxis (3.4%), seasonal allergy (3.4%), anaphylactic shock (2.1%), allergic reaction/hypersensitivity (1.8%), and allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) (1.9%). The other terms were each mentioned in 65 or less clinical trial arms (1.2% or less). These results are visualized in Table 4 below.

Table 4. Hypersensitivity Term Frequency in Cancer Clinical Trial Arms



Lower level terms which indicated severity or included allergen descriptors were used far less often. For example, the term "allergic reaction" can be used to record a hypersensitivity event, however, when using the CTCAE classification system, the term should include a grade level. In the 5595 clinical cancer trial arms, the terms which included a grade descriptor with the adverse

hypersensitivity event were infrequent. Three clinical trial arms (0.05%) used the term "Grade 1 Allergic reaction/hypersensitivity", three arms used the term "Grade 1" Allergic rhinitis, and five arms used "Grade 3 Allergic reaction/hypersensitivity" (0.08%). Two clinical trial arms (0.04%) used the term "hypersensitivity – grade 2". Finally, two clinical trials arms used terms which included grade 4 as a descriptor. A total of 40 clinical trial arms used a hypersensitivity or immune disorder term with a grade level out of the total of 5595 arms in the dataset. The calculated percentage of use in clinical trial arms was 0.7%.

Subset of Severe Anaphylactic and Anaphylactoid Events

A case study of severe adverse events, a subset of anaphylactic and anaphylactoid events, was created. Events with the high-level term "autoimmune disorder" or "hypersensitivity" or "allergic reaction" were not included as it was not possible to determine if these events were of the anaphylactic or anaphylactoid type. Terms included in this data subset were: Anaphylaxis, anaphylactic reactions, anaphylactoid reaction, allergic reaction – anaphylactic, and grade 3-5 allergic reactions. Table 6 below lists the severe hypersensitivity adverse event, the number of affected clinical trial participants, the number of clinical trial participants at risk (exposed to the intervention) and the number of clinical trial arms.

Table 5. Immune Disorder Terms with Adverse Event Severity Grade

Adverse Immune Disorder Event	Count NCT ID	Affected number	At risk number
Autoimmune disorder - grade 1	1	15	15
Autoimmune disorder - grade 2	1	2	15
Autoimmune disorder - grade 3	1	9	15
Autoimmune disorder - grade 4	1	1	15
Gr3 Neturopenia	1	2	5
Grade 1 Allergic reaction/hypersensitivity	3	70	345
Grade 1 Allergic rhinitis	3	103	751
Grade 1 Autoimmune reaction	2	53	668
Grade 1 Rhinitis	4	46	353
Grade 2 Allergic reaction	1	1	30
Grade 2 Allergic reaction/hypersensitivity	1	27	303
Grade 2 Rhinitis	2	20	311
Grade 3 Allergic reaction/hypersensitivity	3	8	345
Grade 3 Allergic/hypersensitivity	2	1	668
Grade 3 Autoimmune reaction	3	6	971
Grade 4 Allergic reaction/Hypersensitivity	1	2	303
Grade 4 Allergy-other	1	1	303
Grade 4 Autoimmune reaction	2	4	668
Hypersensitivity - Grade 2	2	1	38
Hypersensitivity - Grade 3	3	3	74
Leukopenia (Grade 1)	1	1	12
Leukopenia (Grade 2)	1	1	12
Total	40	377	6220

Table 6. Anaphylactic and anaphylactoid Event Subset

Row Labels	Sum of affected_number	Sum of at_risk_number	Count of NCT_id
allergic reaction - anaphylactic	4	47	1
Anaphylactic reaction	153	107488	290
Anaphylactic Reaction to Anti-Thymocyte Globulin	1	57	2
Anaphylactic shock	58	41075	116
Anaphylactoid reaction	9	19814	26
Anaphylaxis	935	29087	193
Anaphylaxtic reaction to erbitux	3	37	1
Angioedema	1	57	1
Bactrim anaphylaxis	1	85	2
Cryoglobulinaemia	1	37	2
Cytokine release syndrome	509	28793	230
Cytokine Release Syndrome (Stem Cell Infusion)	2	6	2
Cytokine Release Syndrome (Thymoglobulin)	1	6	2
Cytokine release syndrome, ATG	12	17	1
Cytokine release syndrome/acute infusion reaction	17	711	27
Cytokine storm	1	207	1
Death	8	66	2
Grade 3 Allergic reaction/hypersensitivity	8	345	3
Grade 3 Allergic/hypersensitivity	1	668	2
Grade 4 Allergic reaction/Hypersensitivity	2	303	1
Grade 4 Allergy-other	1	303	1
Hypersensitivity - Grade 3	3	74	3
Grand Total	**1731**	**229283**	**909**

Description of Terminology and Classification Systems in the case study subset

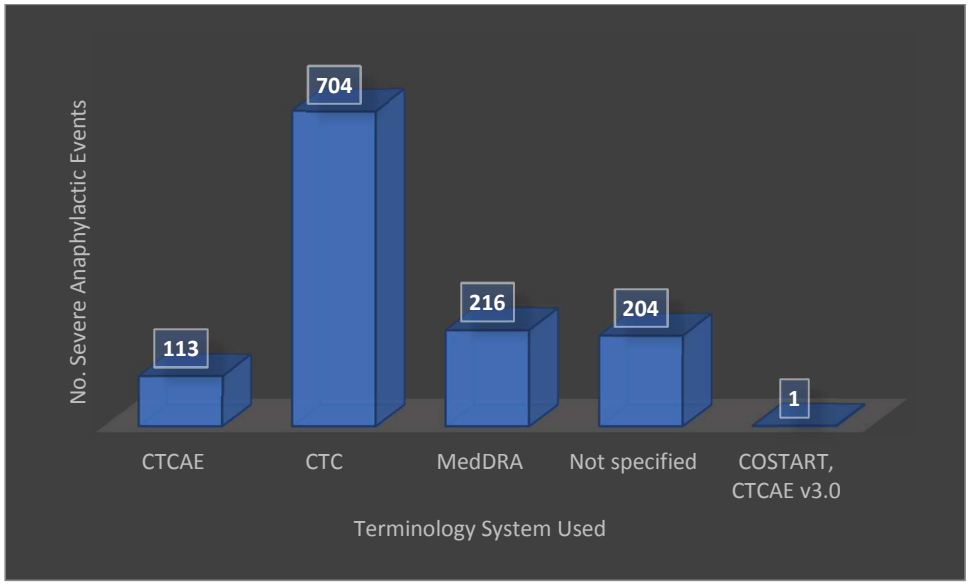
The clinical trial investigators reporting of initial years of clinical trial registration for studies which used CTC were from 2000-2010. No new studies used this classification system after 2010. CTCv2.0 was initially used in 2000 and last used in an update in 2017. CTCv4.0 was initially posted in 2003 and last used in an update in 2019. The next most common type used

was the MedDRA terminology, 28 different versions were used to record these events, however, a MedDRA version was not listed in 39 of the anaphylactic data subset of events. The first time MedDRA was used to report an event was in 2002 and the last time it was used in an update was 2020. The complete list of MedDRA dates by version is available in Appendix A.

CTCAE versions 2.0, 3.0 and 4.0 were used in 48 of the events beginning with year 2003 through last updates in 2019. By version for this data subset, CTCAE 2.0 was first used in 2003 and last used in an update in 2019; CTCAE 3.0 was first used in 2004 and last used in an update in 2019; CTCAE 4.0 was first used in 2003 and last used in an update in 2019. In this data subset of severe anaphylactic type reactions, CTCAE 5.0 was not used at all.

In the data subset of severe anaphylactic or anaphylactoid type hypersensitivity events which totaled 1238 adverse events out of 199,155 exposures (incidence 0.0062), the most commonly used terminology type was Common Toxicity Criteria (CTC). A 704 of the events (56.9%) were recorded with this type of classification system.

Table 7. Anaphylactic and Anaphylactoid Event Terminology or Classification Systems



Severity data element

The ClinicalTrial.gov requires the investigator to enter the adverse events into one of two possible adverse event tables, serious or other (not including serious). The adverse immune disorder events returned from a query of the dataset was divided into these two groups as follows: 2,409 participants experiencing a "serious" immune disorder event and 10,679 participants experiencing an "other (not including serious)" event. Taking the number of participants affected by an event in context with the number of clinical trial participants at risk for an event, less than 1% of clinical trial participants experienced a serious immune disorder event and approximately 1.7% experienced an "other (not including serious)" immune disorder event.

Table 8. Adverse Immune Events in Clinical Cancer Trials (1999-2018)

Adverse Immune Events	Participants Affected	Participants as Risk	% Affected
Serious events	**2409**	**251399**	**0.0096**
Other events	**10679**	**643984**	**0.0166**

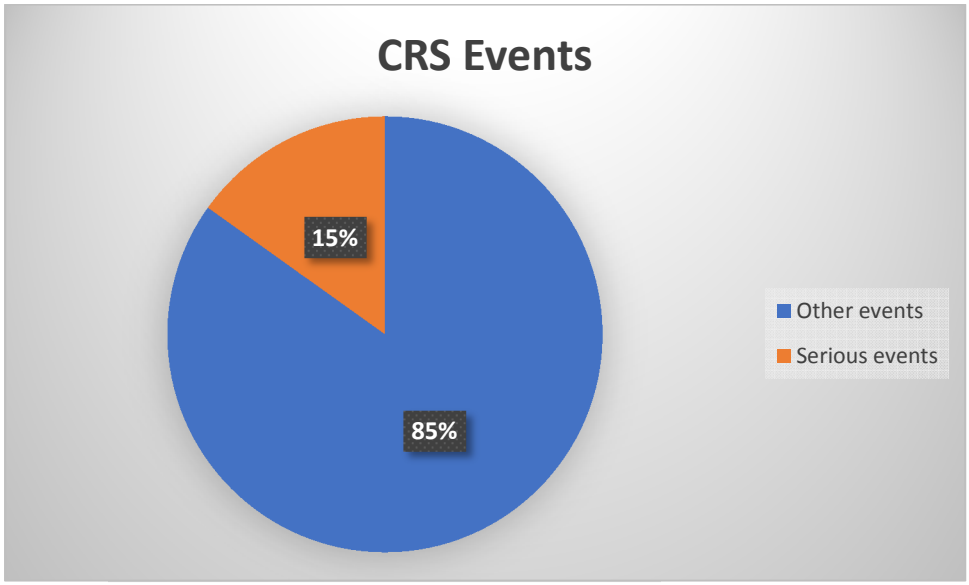
From a clinical trial arm perspective, each clinical investigator selected terms to describe the immune disorder adverse events which occurred in the clinical trial arms. Each clinical trial arm represented a different type of clinical cancer intervention for an NCI trial identification number. Therefore, each clinical trial could report an adverse event incidence for multiple arms in each of the adverse event tables (severe or other than serious). Additionally, a clinical trial could report "0" events for a particular event in a clinical trial arm.

Cytokine Release Syndrome (CRS)

A total of 542 cytokine release syndrome type adverse immune disorder events were reported in this dataset. The terms used to report this type of immune related event were: Cytokine release syndrome, cytokine release syndrome (stem cell infusion), cytokine release syndrome (thymoglobulin), cytokine release syndrome, ATG, cytokine release syndrome/acute infusion reaction, and cytokine storm. The majority of these events (85%) were recorded as other than serious events. However, none of the reactions included a grade level. Although, minimal use of

CTCAE version 4 and no use of CTCAE version 5 (published 2017) (U.S. Department of Health and Human Services, 2017) was recorded and the grade levels for this condition first appeared in version 4.0. Figure 7 below visualizes the percentage of CRS adverse events which were labeled as serious verses other events.

Figure 7. Cytokine Release Syndrome (CRS) Adverse Event Severity



Hypothesis #1

The ability to accurately document severity of anaphylactic and anaphylactoid events secondary to cancer biological or chemotherapy agents is improving with the use of the CTCAE classification system and its emphasis on severity grade levels (1-5) in comparison to MedDRA.

The results indicate this hypothesis is not true. When CTCAE terminology was used to describe severe anaphylactic or anaphylactoid events, the CTCAE grading system was not used. In addition, the severity of the preferred term in the CTCAE classification system to describe anaphylactic events, "anaphylaxis", was often miscoded as "other (not including serious)" instead of "serious" in the data field which allows one of these two permissible values which corresponds to the particular adverse event table (serious or other).

Severity Grading of Anaphylactic or Anaphylactoid Events

ClinicalTrials.gov does not have a severity grading data field, instead the NCI encourages clinical trial investigators to report adverse clinical cancer trial events using the CTCAE classification system, which uses clinical symptoms and signs as criteria to determine the adverse event severity grades levels one through five as discussed in Chapter 2. The grade is then included with the term, for example, Grade 4 Anaphylaxis. (Unified Medical Language System, n.d.) The 48 severe anaphylactic and anaphylactoid adverse events reported using the CTCAE classification system, including versions CTCAE 2.0, CTCAE 3.0, or CTCAE 4.0, did not include a severity grade levels in any of the event terms. CTC, the older version of CTCAE, also did not include severity grade levels in any of the 704 reported events using this classification system. MedDRA did include a grade level in one of the 216 events reported using this terminology system. Only six clinical trial arms were not able to be categorized into the above groups: "Adeers not subm" (1); "COSTART, CTCAE v3.0" (1); "15" (1); "17" (3). It is likely "15" and "17" refer to MedDRA versions, however, this cannot be certain so these were removed from the analysis.

Table 9. Terminology or Classification System and Event Severity Grading

Terminology or Classification System	No Grade	Grade	Total
CTC	704	0	704
MedDRA	215	1	216
CTCAE	48	0	48
Not Specified	190	14	204
Total	1157	15	1172

Severe allergic anaphylactic type events reported with a "not specified" terminology of choice did include grade levels in fourteen clinical trial arms as noted in the table above. The investigators in these cancer clinical trials used the terms "Grade 3 Allergic/hypersensitivity", "Grade 3 Allergic reaction/hypersensitivity", "Grade 4 Allergic reaction/Hypersensitivity" and "Grade 4 Allergy-other". Although, the type of vocabulary or classification system for these terms were not specified, according to the UMLS, the terms are similar to the CTCAE version 3.0 term "Grade 3 Allergic Reaction and Hypersensitivity Including Drug Fever, CTCAE [A29146280/NCI_CTCAE_3/PT/C54752]" and "Grade 4 Allergic Reaction and Hypersensitivity Including Drug Fever, CTCAE [A29160643/NCI_CTCAE_3/PT/C54757]" (Unified Medical Language System, n.d.)

A Fisher's Exact Test was used to test the statistical difference due to category totals < 5. Interestingly, the clinical trials which did not specify their terminology or classification system of choice were significantly more likely to include the grade level in comparison to the MedDRA terminology described events with grades levels (Fisher exact test statistic = 0.0003, $p < 0.05$). This also held true for the comparison between the "not specified" terminology events and the CTC classification system term events with grade levels (Fisher exact test statistic value <0.00001, $p < 0.05$). There was no statistical different between the CTCAE classification system

and the "not specified" terminology events, (Fisher exact test statistic value = 0.0786, $p < 0.05$), however, it may have been secondary to a lower number of events in the CTCAE category.

Table 10. Terminology Grading

Term	No Grade	Grade	Totals
CTC	704	0	704
MedDRA	215	1	216
CTCAE	48	0	48
Not Specified	190	14	204
Totals	1157	15	1172
Fisher's Exact Tests			
	No Grade	**Grade**	**Marginal Row Totals**
MedDRA	215	1	216
CTCAE	48	0	48
Marginal Column Totals	263	1	264(Grand Total)
The Fisher exact test statistic value is 1. The result is *not* significant at p < .05.			
	No Grade	**Grade**	**Marginal Row Totals**
CTCAE	48	0	48
Not Specified	190	14	204
Marginal Column Totals	238	14	252 (Grand Total)
The Fisher exact test statistic value is 0.0786. The result is *not* significant at p < .05.			
	No Grade	**Grade**	**Marginal Row Totals**
CTC	704	0	704
CTCAE	48	0	48
Marginal Column Totals	752	0	752(Grand Total)
The Fisher exact test statistic value is 1. The result is *not* significant at p < .05.			
	No Grade	**Grade**	**Marginal Row Totals**
MedDRA	215	1	216
Not Specified	190	14	204
Marginal Column Totals	405	15	420(Grand Total)

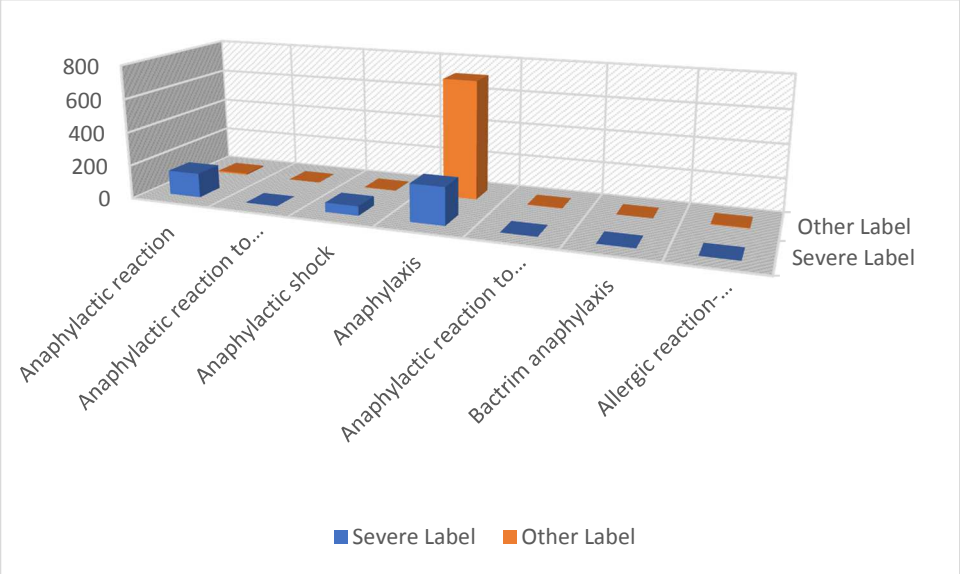
The Fisher exact test statistic value is 0.0003. The result is significant at p < .05.			
	No Grade	**Grade**	**Marginal Row Totals**
CTC	704	0	704
Not Specified	190	14	204
Marginal Column Totals	894	14	908 (Grand Total)
The Fisher exact test statistic value is < 0.00001. The result is significant at p < .05.			

(Stangroom, 2020)

Accuracy

Additionally, the CTCAE preferred term for anaphylactic events, "anaphylaxis", was miscoded as an "other (not including serious)" event the majority of the time in the ClinicalTrials.gov dataset. "Anaphylaxis" was only labeled correctly as a severe event 222/935 (23.7%) of the time. This term was coded in the dataset using CTCAE in the majority of these events, that is the investigator indicated their controlled terminology or classification system of choice as being CTCAE versions 2.0, version 3.0, or version 4.0. In contrast, the use of the MedDRA term "anaphylactic reaction" was miscoded far less as an "other (not including serious)" event. This reporting error occurred in only 5% of its use in this dataset as shown in Table 11 below.

Table 11. Anaphylactic Terms Miscoded as Other (Not including Serious)



Using a chi square test, the proportion of investigator correct identification of the MedDRA term "anaphylactic reaction" as a severe immune disorder adverse event was compared with the proportion of investigator correct identification of the CTCAE term "anaphylaxis" as a severe immune disorder adverse event. The results indicate that there is a significant difference in the correct identification of an anaphylactic event as severe when using the MedDRA term "Anaphylactic reaction" (92.3% correct) in comparison to using the CTCAE term "Anaphylaxis" (23.8% correct, p-value < 0.001). See the Table 12 below for the category counts and chi square value.

Table 12. Comparison of Accuracy of Severity by Term Use

Term	Severe	Other	Total	P-Value
Anaphylactic reaction	145	12	157	
Anaphylaxis	223	713	936	
Total	368	725	1093	1.8939E-63

Cytokine Release Syndrome (CRS) Severity Reporting

The severity of CRS events was coded using the permissible values, serious or other (not including serious). CRS is a variable condition, therefore, CTCAE does allow grading at all five levels. Therefore, it was not possible to determine if the event was correctly coded or not as a serious event without having direct access to the original data. Table 13 below lists the adverse event terms and the proportion of severe and not severe events per term used to describe these adverse events.

As noted above in the descriptive analysis, no severity grading levels were reported with the terms used to describe cytokine release syndrome or acute infusion reactions. Although, the CTCAE classification has terms available to describe severity grades by symptom criteria and oxygen requirements, for example “Grade 3 Cytokine Release Syndrome [C4686146]”. (Unified Medical Language System, n.d.)

Table 13. Cytokine Release Syndrome Event Severity

Term	Serious	Other	Total
Cytokine release syndrome	78	431	509
Cytokine release syndrome (Stem Cell Infusion)	0	2	2
Cytokine release syndrome (Thymoglobulin)	0	1	1
Cytokine release syndrome, ATG	0	12	12
Cytokine release syndrome/acute infusion reaction	4	13	17
Cytokine storm	1	0	1
Total	83	459	542

Hypothesis #2

Severe anaphylactic and anaphylactoid events recorded in ClinicalTrials.gov rarely (<5% of events) include the allergen responsible for the event which hinders the ability to study incidence when multiple drug or multiple therapeutic agents are used in clinical cancer trials. In other words, there is no statistical difference between the most common terminologies used in this database regarding the inclusion of the drug allergen in the allergic event term.

This hypothesis is true when analyzing the events which included the terminology or classification system name. As expected, the most commonly used terminologies and classification systems by the investigators did not support the inclusion of a drug or biological allergen. MedDRA, CTC and CTCAE did not have the ability to capture the allergen responsible for the event. Only two other systems were noted Adeers and COSTART which were used in one arm each and also did not note allergens within the terms. The majority of severe anaphylactic and anaphylactoid events were recorded by clinical investigators using CTC

and all of the 704 events reported with this classification system used the term was "anaphylaxis".

Additionally, in this subset of severe events, several of the clinical trial investigators did not specify the terminology or classification system used. However, a few of the events in this "not specified" category included the allergen responsible for the severe allergic event (5/204). In other words, the only allergens recorded in any of the severe anaphylactic and anaphylactoid events were the adverse events in which the terminology or classification system was not specified by the clinical investigator. For example, "Bactrim anaphylaxis" was used to describe an anaphylactic event. The only other terms noted to have the allergen included were "anaphylactic reaction to Erbitux" and "anaphylactic reaction to anti-thymocyte globulin", as shown in Table 14 below.

Table 14. Inclusion of Allergen with Anaphylactic and Anaphylactoid Events

Terminology or Classification System	Allergen	No Allergen	Total
CTCAE	0	48	48
CTC	0	704	704
MedDRA	0	216	216
Unspecified	5	199	204

Table 15. Fisher's Exact Tests Comparing Allergen Inclusion

Results

	Allergen	No Allergen	***Marginal Row Totals***	
CTCAE	0	48	48	
CTC	0	704	704	
Marginal Column Totals	0	752	752 (Grand Total)	

Fisher exact test statistic value = 1. The result is *not* significant at p < .05.				
Results				
	Allergen	No Allergen	***Marginal Row Totals***	
CTCAE	0	48	48	
MedDRA	0	216	216	
Marginal Column Totals	0	264	264 (Grand Total)	
Fisher exact test statistic value = 1. The result is *not* significant at p < .05.				
Results				
	Allergen	No Allergen	***Marginal Row Totals***	
CTCAE	0	48	48	
Unspecified	5	199	204	
Marginal Column Totals	5	247	252 (Grand Total)	
The Fisher exact test statistic value = 0.5867. The result is *not* significant at p < .05.				
Results				
	Allergen	No Allergen	***Marginal Row Totals***	
MedDRA	0	216	216	
Unspecified	5	199	204	
Marginal Column Totals	5	415	420 (Grand Total)	
The Fisher exact test statistic value = 0.0264. The result is significant at p < .05.				
	Allergen	No Allergen	***Marginal Row Totals***	
MedDRA	0	216	216	
CTC	0	704	704	
Marginal Column Totals	0	920	920 (Grand Total)	
The Fisher exact test statistic value = 1. The result is *not* significant at p < .05.				

	Allergen	No Allergen	***Marginal Row Totals***	
CTC	0	704	704	
Not Specified	5	199	204	
Marginal Column Totals	5	903	908 (Grand Total)	
The Fisher exact test statistic value = 0.0006. The result is significant at p < .05.				

Table 16. Cytokine Release Syndrome Terms and Severity

Term	Serious	Other	Total
Cytokine release syndrome	78	431	509
Cytokine release syndrome (Stem Cell Infusion)	0	2	2
Cytokine release syndrome (Thymoglobulin)	0	1	1
Cytokine release syndrome, ATG	0	12	12
Cytokine release syndrome/acute infusion reaction	4	13	17
Cytokine storm	1	0	1
Total	83	459	542

Although, there seems to be a trend noting the lack of notation of an allergen with CRS severe events in comparison to CRS other than serious events, the statistical comparison using a Fisher's exact test between the categories was not significant ($p < 0.05$).

Table 17. Cytokine Release Syndrome Event Allergen Inclusion and Severity

	Allergen Included	No Allergen Included	Total	Fisher exact test value
CRS Serious Events	0	83	83	
CRS Other Events	15	431	446	
Total	15	514	529	0.1442

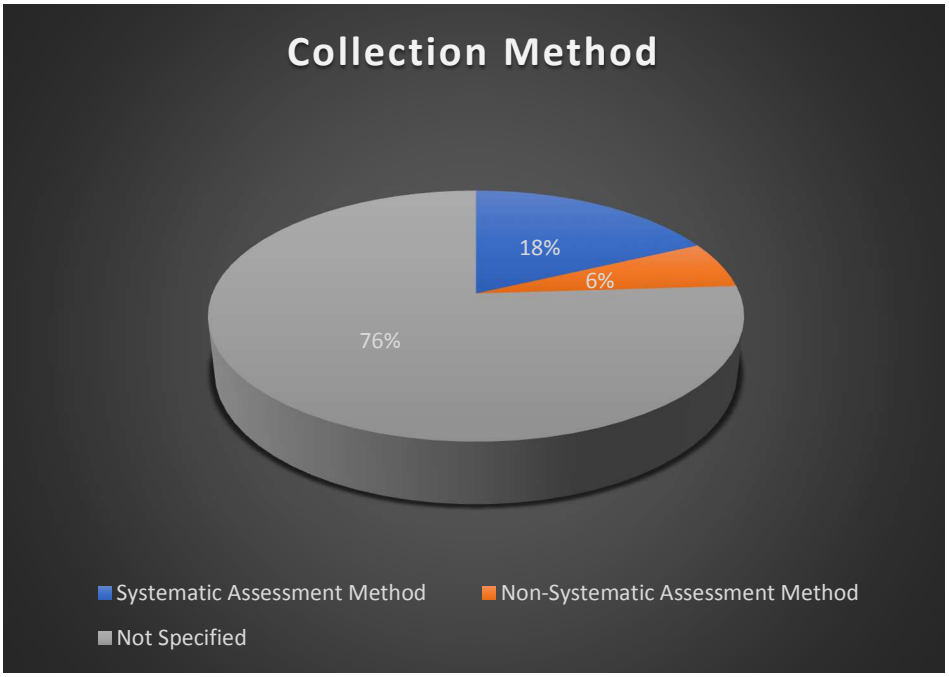
(Stangroom, 2020)

Hypothesis #3

Over 25% of the severe allergic events have not been recorded using a systematic assessment method which could result in underreporting of events.

The hypothesis was found to be true as only 18% of the subset of severe anaphylactic and anaphylactoid events were collected using a systematic collection method. However, this hypothesis is difficult to assess completely due to the large number of adverse events in the severe anaphylactic or anaphylactoid data subset labeled as "not specified" in the collection method data field. Over 75% of the events were collected with a "not specified" method, 18% were collected using a systematic assessment method and 6% were collected using a non-systematic collection method as noted in the pie graph in Figure 8 below.

Figure 8. Collection Method of Anaphylactic and Anaphylactoid Events



However, the collection methods varied by terminology or classification system. In this data subset, 877/937 (93.6%) events including the term "anaphylaxis" (primarily used with CTC and CTCAE classification systems) were collected using an unspecified collection method. In contrast, only 6/157 (3.8%) of terms labeled as "anaphylactic reaction", primarily a MedDRA terminology term, were collected with an unspecified collection method. In fact, 107/157 (68.2%) of events labeled using the term "anaphylactic reaction" were collected using a systematic assessment method. However, 44/157 (28%) of the "anaphylactic reaction" events were collected with a non-systematic assessment method. This remains consistent with the hypothesis that over 25% would be collected using a non-systematic method. Tables 17 visualizes the terms and their collection methods. Table 18 below lists the exact numbers by term and collection assessment method.

Table 18. Visualization of Anaphylactic and Anaphylactoid Term Collection Methods

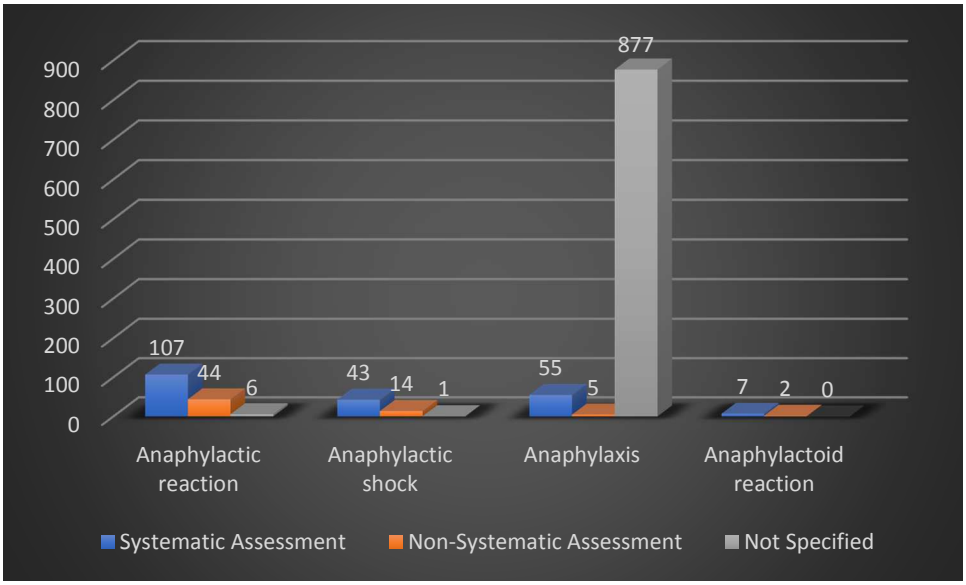


Table 19. Severe Anaphylactic Type Adverse Events by Collection Methods Categories

	Systematic Assessment	Non-Systematic Assessment	Not Specified	Total
Anaphylactic reaction	107	44	6	157
Anaphylactic shock	43	14	1	58
Anaphylaxis	55	5	877	937
Anaphylactoid reaction	7	2	0	9
Total	212	65	884	1161

A Chi Square test was used to analyze if there is a significant difference between the categories of collection method (systematic assessment, non-systematic assessment or not specified) and investigator selected term of choice. There was a significant difference in assessment methods when all categories were tested, including not specified was tested (p value < 0.05) shown in Table 19 below. When just testing for a significant difference between the terms and assessment method categories without the "unspecified" category, the p value remained significant at 0.0012 shown in Table 20 below.

Table 20. Chi Square Test of Collection Method and Term Categories

Chi Square				
Observed	**Systematic Assessment**	**Non-Systematic Assessment**	**Not Specified**	**Total**
Anaphylactic reaction	107	44	6	157
Anaphylactic shock	43	14	1	58
Anaphylaxis	55	5	877	937
Anaphylactoid reaction	7	2	0	9
Total	212	65	884	1161
P-value	1.4816E-175			

Expected	Systematic Assessment	Non-Systematic Assessment	Not Specified	Total
Anaphylactic reaction	28.66838932	8.789836348	119.5417743	157
Anaphylactic shock	10.59086994	3.247200689	44.16192937	58
Anaphylaxis	171.0973299	52.45908699	713.4435831	937
Anaphylactoid reaction	1.643410853	0.503875969	6.852713178	9
Total	212	65	884	1161

Table 21. Chi Square Test of Collection Method and Terminology Categories without Unspecified Values

Chi Square Without Not Specified Category

Observed	Systematic Assessment	Non-Systematic Assessment	Totals
Anaphylactic reaction	107	44	151
Anaphylactic shock	43	14	57
Anaphylaxis	55	5	60
Anaphylactoid reaction	7	2	9
Totals	212	65	277
P-value	0.001222425		
Expected	Systematic Assessment	Non-Systematic Assessment	
Anaphylactic reaction	115.566787	35.433213	151
Anaphylactic shock	43.62454874	13.37545126	57
Anaphylaxis	45.92057762	14.07942238	60
Anaphylactoid reaction	6.888086643	9	9
Total	212	65	277

Figure 9 uses a pie graph to visualize the large number of anaphylactic and anaphylactoid events in which the clinical investigator did not specify their collection method as either systematic or non-systematic. Figure 10 displays the information in a pie graph using only the specified collection methods.

Figure 9. Pie Graph Displaying Anaphylactic and Anaphylactoid Adverse Event Collection Methods

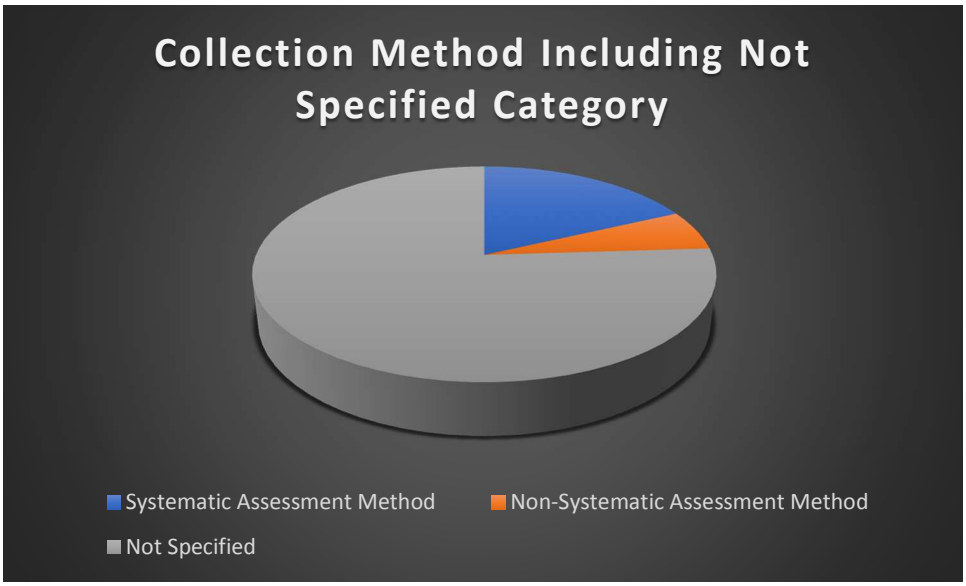
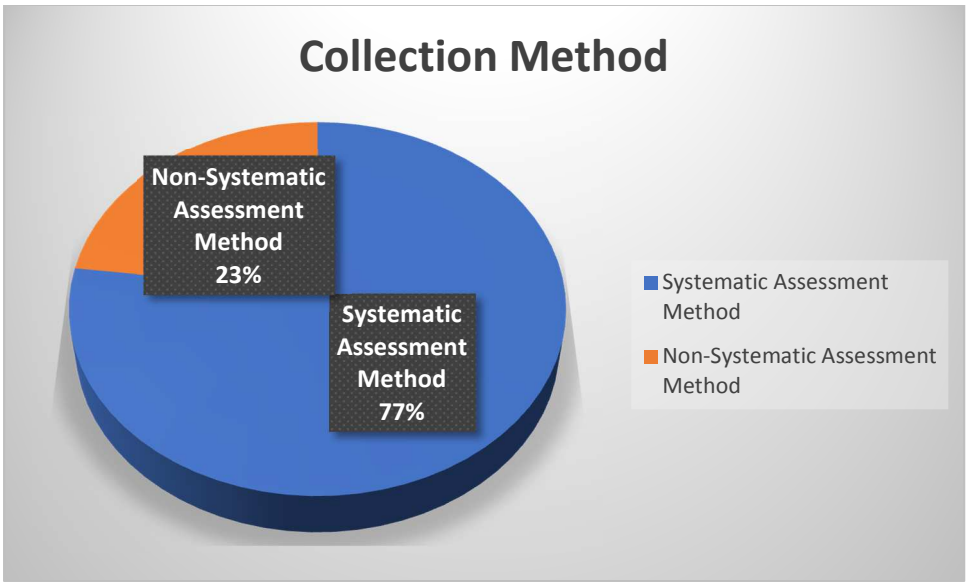


Figure 10. Pie Graph Displaying Anaphylactic and Anaphylactoid Adverse Event Collection Method without Not Specified Category



Chapter V. Discussion

Cancer clinical trials involve complex treatment interventions and often these interventions involve a combination of both biologic therapies (monoclonal antibodies) and chemotherapies. Monitoring adverse events involving new cancer therapies is important for patient safety especially potentially life-threatening hypersensitivity reactions. Population level research can aid in providing frontline health providers such as physicians, nurses, and physician assistants with knowledge of potential predictors and risk factors for severe hypersensitivity reactions which can improve clinical cancer therapy and provide at-risk patients with screening and desensitization therapies if necessary to maintain first line therapies for cancer treatment. Furthermore, population level research can increase the power of studies of rare disease with meta-analysis methods. The adverse hypersensitivity event data from these trials can improve emergency preparedness for life-threatening infusion reactions (cytokine release syndrome), anaphylactic or anaphylactoid reactions. Unfortunately, the current process for collecting and recording the characteristics of these types of events is fault with poor granularity, inaccuracies in severity, missing information, controlled terminology challenges and inconsistent collection methods.

The findings of this study indicate that several gaps exist in reporting of cancer clinical trial hypersensitivity events, especially severe anaphylactic and anaphylactoid events. The specific areas of concern in clinical trial severe hypersensitivity event reporting were the accuracy of reporting the hypersensitivity event severity when using the CTCAE preferred term "anaphylaxis", the lack of investigator use of the CTCAE severity grading system, and the lack

of ability to capture the drug allergen responsible for the severe anaphylactic, anaphylactoid or CRS related adverse events in multi-drug therapies. Furthermore, a large portion of clinical cancer trials either did not report their adverse event collection method or do not use a systematic assessment method of collecting these adverse events which could lead to under reporting of these events.

Granularity

An overall analysis of the terms used in clinical trial reporting of immune disorder adverse events indicates the most common term used to describe cancer immune disorder adverse events was "hypersensitivity". This term was used to describe 22.2% of the immune adverse events over the nine year study period in which the data in this dataset was entered into ClinicalTrials.gov. Hypersensitivity is a high-level term which lacks necessary descriptors to perform adequate pharmacovigilance of drug or biological agent monitoring of immune disorder events during clinical trials. The term does indicate the event severity or whether the event was allergic or non-IgE in pathophysiology. Furthermore, this term does indicate the etiology or allergen responsible for the hypersensitivity event occurring while the patient is receiving a clinical trial intervention which often involve multiple drugs, biological agents and/or other therapies such as radiation and surgery. In other words, without any further information, this term alone will not aid in surveillance of drug or biological agent adverse hypersensitivity events in clinical cancer trials. It may be the information which may have existed in the original investigator data has not been adequately transferred to the ClinicalTrials.gov database and therefore, not available to health consumers who may be searching for a potential clinical trial to participate in.

Hypothesis #1

The ability to accurately document severity of anaphylactic and anaphylactoid events secondary to cancer biological or chemotherapy agents is improving with the use of the CTCAE classification system and its emphasis on grade levels (1-5) in comparison to MedDRA.

The results of the data analysis for hypothesis one indicates the use of the NCI CTCAE classification system has not improved the ability to capture severity and has resulted in further challenges in reporting severity level accuracy of anaphylactic events in clinical cancer trials. This is indicated by the lack of clinical investigator use of the classification system's grades to capture the severity of these types of adverse events even with these terms available in the CTCAE versions used in these clinical trials. In summary, clinical cancer trial investigators used CTCAE terms which did not include the severity grading levels to describe these severe anaphylactic and anaphylactoid adverse events. For example, an investigator may report "Anaphylaxis, CTCAE [A29138945]" instead of "Grade 4 Anaphylaxis [A29149366]". (National Cancer Institute, n.d.)

Furthermore, the results indicate that the use of the most common term in this classification system to describe severe anaphylactic events, "anaphylaxis", has resulted in significantly more errors in mislabeling anaphylactic events as "other (not including serious)" events in comparison to the MedDRA classification system's most common term to describe these events, "anaphylactic reaction". As discussed in Chapter 2, the CTCAE classification system grading severity levels only allow for the grading of "anaphylaxis" at grade levels three (severe), four

(life-threatening) and five (death). Therefore, these events should only be included in the severe event table in ClinicalTrails.gov. However, this was not the case as the results indicate there were significantly more CTCAE "anaphylaxis" events entered into the "other (not including serious)" table in comparison to the MedDRA terminology equivalent term "anaphylactic reaction" which was rarely mislabeled. The possibility exists that the definition of the term "anaphylaxis" is not as well understood by clinical investigators in comparison to the MedDRA term. Another possibility is the clinical investigators are labeling the severe grade 3 events which are described in the CTCAE version 4.0 Quick Reference as "severe or medically significant but not immediately life-threatening" as other than serious events due to the existence of only two permissible severity levels (severe or other) in this database. (U.S. Department of Health and Human Services, 2008)

The lack of use of severity grading levels and the incorrect labeling of these events will impact the ability of public health and clinical research informatics investigators to study these severe events on a population level across clinical trials. First and foremost, the ClinicalTrials.gov data will not be able to distinguish which clinical trial participants developed adverse hypersensitivity reactions which required immediate intervention for potentially life-threatening situations and study potential predictors for these events. Secondly, the adverse events which resulted in death may not be captured correctly by the data without the level 5 designation which directly associates the hypersensitivity reaction with the adverse event. Finally, if the population level researcher used only the severe adverse event table to study these severe events, the investigator would inadvertently not capture a large number of mislabeled events in the "other (not including

serious) table. This would result in a much lower incidence rate of severe anaphylactic events secondary to clinical cancer trial drug and biological interventions.

Hypothesis #2

Severe allergic events recorded in ClinicalTrials.gov rarely (<5% of events) include the allergen responsible for the event which hinders the ability to study incidence when multiple drug or multiple therapeutic agents are used in clinical cancer trials. In other words, there is no statistical difference between the most common terminologies used in this database regarding the inclusion of the drug allergen in the allergic event term.

The first part of this hypothesis is true. All terminology and classification systems, in addition to the events in which the terminology or classification system was not specified, rarely reported the allergen responsible for adverse event. This was expected due to the terminology and classification systems used in capturing the severe anaphylactic and anaphylactoid events. CTC, CTCAE, and MedDRA did not have the ability to code the event and the drug or biological agent responsible for the event. However, in studying the adverse event table arms, there was not an ability to link the particular hypersensitivity event to a single drug in the multi-drug intervention arms. For example, in Clinical Trial NCT00036738 which studies drug and radiation interventions for leukemia, the single arm trial treatment is listed as including the following:

> **Arm/Group Title Treatment (Allogeneic Nonmyeloablative HSCT)**
> **Arm/Group Description:**
> -Cyclosporine: Given IV or PO
> -Dasatinib: Given PO
> -Fludarabine Phosphate: Given IV
> -Imatinib Mesylate: Given PO
> -Mycophenolate Mofetil: Given PO
> -Nilotinib: Given PO

-Nonmyeloablative Allogeneic Hematopoietic Stem Cell Transplantation: Undergo nonmyeloablative allogeneic PBSC transplantation
-Peripheral Blood Stem Cell Transplantation: Undergo allogeneic PBSC transplantation
-Therapeutic Allogeneic Lymphocytes: Given IV
-Total-Body Irradiation: Undergo TBI (U.S. National Library of Medicine, 2020)

In this trial, one anaphylaxis event was record in the "Other (Not Including Serious) Adverse Events Table", however, the treatment interventions for this arm in the table was only listed as "Allogenic Nonmyeloablative HSCT". Therefore, it was not possible to determine which intervention was the etiology of this event. Generally, with severe hypersensitivity events, especially anaphylactic type events, there will be a close time association between the administration of the drug or agent and the event. Therefore, without the ability to record or effectively link the drug or agent intervention to the event, this information will be lost in the transfer of the clinical trial data from the clinical investigator to the NLM ClinicalTrials.gov database. The use of a terminology system such as RxNorm, which can capture the drugs in relation to the events could be helpful. Furthermore, the use of a term which has the ability to enter in a specific drug or biological agent with the event, such as the recent guidance for collection of adverse infection events related to COVID-19. On March 25, 2020, the Department of Health & Human Services Memorandum advised clinical investigators to use the term "Infections and infestations – Other, specify; specify = COVID-19". (Mooney, Moscow, Ivy, & McCaskill-Stevens, 2020) A similar approach could be used to capture the drug etiology or biological agent associated with the hypersensitivity event in clinical cancer trials. For example, an additional field could be added for the immune category which requires the clinical investigator to specify which drug or agent was related or the likely etiology of the hypersensitivity event. Interestingly in NCT00040485, a similar terminology method was used

to record a blood infection, “Infections and Infestations -Other (Blood). (U.S. National Library of Medicine, 2020)

Regarding the second part of the hypothesis, there was no statistical difference between CTCAE, CTC and MedDRA with regards to inclusion of allergen discriptors within the adverse event term, however, there was a small statistical significant difference between the severe anaphylactic terms recorded using MedDRA terminology and those terms recorded with an unspecified terminology. Statistical significance was also found between the categories of anaphylactic terms recorded using the CTC classification which included an allergen in comparison to the terms recorded using an unspecified terminology which included the allergen. This significance may be due to the increase in flexibility of clinical investigators entering free text within the adverse event tables. For example, the term “Bactrim Anaphylaxis” was used which in not in the UMLS system, however, easily identified the cause of the anaphylactic reaction, the antibiotic sulfa drug, Bactrim.

Hypothesis #3

Over 25% of the severe allergic events have <u>not</u> been recorded using a systematic assessment method which could result in underreporting of events.

The final hypothesis 3 was true, however, a large number of the clinical trials did not indicate their method of collecting adverse events. In fact, a striking number of these trials, 76%, did not report their method of assessment. Of the remaining 24% of clinical trials which did report collection methods for severe anaphylactic and anaphylactoid events, approximately 75%

collected their adverse events using a systematic assessment method. Therefore, if you remove the unspecified category, the rate of systematic assessment collection method for cancer clinical trial severe anaphylactic and anaphylactoid adverse events was equal to 25%.

The events recorded using the term "anaphylaxis" did not report their adverse event collection method for immune disorders in 93.6% of the cases, the overwhelming majority of cases. This was in contrast to the MedDRA terminology reported events which used a systematic assessment collection method in the majority of cases (68.2%). Therefore, investigators using MedDRA terminology were significantly more likely to report the use of a systematic method of assessment for adverse events, however, it is difficult to determine which terminology or classification system is more likely to use a systematic method given the large number of unspecified method type data points for events coded using the CTCAE and CTC classification systems.

The impact of using a non-systematic collection method for adverse event reporting is the potential for not capturing events. In a non-systematic assessment collection method, adverse immune events were not solicited by the clinical investigators and therefore, the events may or may not be reported by the clinical trial participant. In a systematic assessment approach, the clinical investigators use a protocol or pre-determined method to periodically assess for potential adverse events such as a questionnaire or a diary. (National Institute of Health, 2020) Therefore, without a protocol, even emergency room visits may be forgotten and not reported during the regularly scheduled clinical trial visits. Under reporting of severe hypersensitivity events could

lead to inaccurately high drug safety assessments. Therefore, the importance of rigorous adverse event collection methods of severe events cannot be overstated.

Study Limitations

As discussed above, a significant limitation of the study is the high number of severe anaphylactic events which were recorded using an unspecified terminology or classification system.

Chapter VI. Conclusion

The NCI CTCAE classification system was not found to improve the capture of severe hypersensitivity events in the case study of anaphylaxis and anaphylactoid events. Lack of clinical investigator adoption of CTCAE terms with grades contributed to the inability to capture the severity level of anaphylactic or anaphylactoid events and resulted in no improvement in comparison to the previous use of CTC and MedDRA systems. Furthermore, the CTCAE use of the term "anaphylaxis" resulted in a significant increase in miscoding of this adverse event severity level in comparison to the MedDRA equivalent term. Furthermore, the lack of identification of the allergen etiology through the use of a term descriptor for these events in multi drug or multi interventional trials continues to be a significant problem which hinders the ability to use this data on a populations level for pharmacovigilance. The overwhelming majoring of allergic reaction terms did not include the allergen and therefore, in dual or multi- drug therapies, the etiologic agent was not identifiable.

To address these barriers to population level research of severe hypersensitivity events in clinical cancer trials, further research should be done to analyze the reason for lack of investigator adoption of the NCI CTCAE severity grade levels in severe hypersensitivity events. Furthermore, a return to the use of the MedDRA term "anaphylactic reaction" should be considered to avoid severity level confusion as this could make a significant impact on capturing severity events in research. Also, further study and updating of CTCAE terms with a high percentage of miscoding of severity levels should be considered. Furthermore, adapting terms which include the drug or at least the drug class could significantly improve the ability to capture

hypersensitivity event etiology. This could advance the quality of data in population level study of anaphylaxis etiology and incidence in multi-drug cancer therapy, therefore, making a significant impact on the safety of these drugs. Finally, systematic assessment adverse event collection methods should be used in clinical trials to reduce the possibility of underreporting of adverse hypersensitivity events.

Chapter VII. References

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Appendix A: Cancer Drug and Biological Intervention Terms List

Intervention	Drug Class	Alternative names	Abbreviation	Code name
cyclophosphamide	alkylatingAgent	Ciclofosfamida,Ciclofosfamida, Ciclofosfamide, Clafen, Claphene, CP monohydrate, Cyclophospham, Cyclophosphamid monohydrate, Cyclophosphamidum, Cyclophosphan, Cyclophosphanum, Cytophosphane, Genoxal, Syklofosfamid	CTX	WR-138719
etoposide	plantAlkaloid	Demethyl Epipodophyllotoxin Ethylidine Glucoside epipodophyllotoxin	EPEG	VP-16, VP-16-213
cytarabine	antimetabolite	.beta.-Cytosine arabinoside, arabinofuranosylcytosine, arabinosylcytosine, aracytidine, beta-cytosine arabinoside, cytarabine hydrochloride, cytarabinum, cytosine arabinoside, cytosine arabinosine hydrochloride,cytosine-.beta.-arabinoside, Tarabine PFS	ARA-C	CHX-3311, U 19920, U-19920, U-29920A HCl, WR-28453
cetuximab	monoclonalAB	Anti-EGFR Monoclonal Antibody, Anti-Epidermal Growth Factor Receptor Monoclonal Antibody, C225 monoclonal antibody, Chimeric Anti-EGFR Monoclonal Antibody, Chimeric Monoclonal Antibody C225, anti-(human epidermal growth factor receptor) (human-mouse monoclonal C225 gamma1-chain), disulfide with human-mouse monoclonal C225 kappa-chain, dimer monoclonal antibody C225, Erbitux	Chimeric MoAb C225, MOAB C225	C225, IMC-C225
vincristine sulfate	plantAlkaloid	leurocristine sulfate, vincristine sulfate, Vincosid, Vincasar PFS	VCR	
vincristine sulfate liposome	plantAlkaloid	liposomal vincristine sulfate, vincristine liposomal, vincristine sulfate liposome injection, marqibo		
dexamethasone	steroid	Desamethasone, Dexamethasonum, disaimisong, DXM, Hexadecadrol, Maxidex, Methylfluorprednisolone	DM	
methotrexate	antimetabolite	alpha-methopterin, amethopterin, methotrexate methylaminopterin, Methotrexatum, methylaminopterin, Metotrexato	MTX	CL-14377, WR-19039

prednisone	steroid	delta 1-cortisone, Delta(1)-Cortisone, deltacortisone, deltadehydrocortisone, metacortandracin, PRD, Prednisonum	PRED	
doxorubicin	anthracycline	doxorubicin hydrochloride, ADR, adriamycin, adriamycin hydrochloride, Adriamycine, chloridrato de doxorrubicina, doxorubicin.HCl, hydroxydaunorubicin	ADM, Adria, DOX	FI-106
fludarabine	antimetabolite	fludarabine phosphate, fludarabine monophosphate	2-F-ara-AMP	SH T 586
cisplatin	platinum	CACP, cis-DDP, cis-diamminedichloridoplatinum, cis-diamminedichloro platinum (II), cis-diamminedichloroplatinum, Cis-dichloroammine Platinum (II), Cismaplat, Cisplatina, cis-platinous diamine dichloride, cis-platinum, cis-platinum II, cis-platinum II diamine dichloride, CPDD, Cysplatyna, DDP, PDD, Peyrone's Chloride, Peyrone's Salt, Platinoxan, platinum diamminodichloride, Platinol, Platinol-AQ	CDDP, DDP	
paclitaxel	taxane	Taxol	TAX	
liposomal paclitaxel	taxane	LEP, liposome-encapsulated paclitaxel, paclitaxel liposome, LEP-ETU	PNU-93914	
rituximab	monoclonalAB	BI 695500, C2B8 Monoclonal Antibody, CT-P10, IDEC-C2B8 monoclonal antibody, rituximab biosimilar ABP 798, rituximab biosimilar BI 695500, rituximab biosimilar GB241, rituximab biosimilar HLX01, rituximab biosimilar IBI301, rituximab biosimilar PF-05280586, rituximab biosimilar Reditux, rituximab biosimilar RTXM83, rituximab biosimilar SAIT101, Rituxan	MOAB IDEC-C2B8	

methylprednisolone	steroid	methylprednisolone acetate, methylprednisolone succinate, methylprednisolonum, Depo-Medrol, Medlone 21, Medrol, Meprolone, Metrocort, Metypred, Solu-Medrol, Summicort	MePRDL	
docetaxel	taxane	Docefrez, Taxotere, Taxotere injection concentrate	TXT	RP 56976
leucovorin	chemoprotectant	leucovorin calcium, calcium (6S)-folinate, calcium folinate, CFR, citrovorum factor, folinate calcium, folinic acid, Folinic Acid Calcium Salt Pentahydrate, Leucovorin, LV, Wellcovorin	CF	
bendamustine	alkalatingAgent	bendamustin hydrochloride, CEP-18083, cytostasan hydrochloride, Treanda		SDX-105
everolimus	mTORInhibitor	42-O-(2-hydroxy)ethyl rapamycin, Afinitor, Zortress		RAD001
melphalan	alkalatingAgent	L-phenylalanine mustard, L-sarcolysin, L-sarcolysin phenylalanine mustard, L-sarcolysine, phenylalanine mustard, phenylalanine nitrogen mustard, sarcoclorin, Alkeran	L-PAM	CB-3025, WR-19813
daunorubicin	anthracycline	daunorubicin hydrochloride, cloridrato de daunorubicina, daunoblastine, daunomycin hydrochloride, rubidomycin hydrochloride, Cerubidine		FI-6339, RP-13057
busulfan	alkylatingAgent	BSF, Bussulfam, Busulfanum, busulphan, glyzophrol, methanesulfonic acid, tetramethylene ester, Myeleukon, Myeloleukon, Myelosan, Mylecytan, Sulfabutin, tetramethylene bis(methanesulfonate),Busulfex Myleran	BU, BUS	CB-2041, GT-41, WR-19508
sirolimus	mTORInhibitor	rapamycin, Rapamune	RAPA, SLM	AY 22989, SILA 9268A, WY-090217
dasatinib	tyrosineKinaseInhibitor	Sprycel		BMS-354825

sorafenib	tyrosineKinaseInhibitor	sorafenib tosylate, Nexavar	SFN	BAY 54-9085
vinorelbine	plantAlkaloid	vinorelbine tartrate, navelbine ditartrate, vinorelbine ditartrate, Navelbine	NVB	KW-2307
ifosfamide	alkalatingAgent	Ifomide, Iphosphamid, iphosphamide, Isoendoxan, Iso-Endoxan, isophosphamide, Naxamide, Cyfos, Ifex, Ifosfamidum	IFF, IFO, IFX, IPP	Asta Z-4942, MJF-9325, Z-4942
carboplatin	platinum	Carboplatin Hexal, Carboplatino	CBDCA	JM-8
ixabepilone	antimicrotubuleAgent	Azaepothilone B, epothilone B lactam, Epothilone-B BMS 247550, Ixempra		BMS-247550
asparaginase	enzyme	ASP-1, asparaginase II, Colaspase, L-ASP, L-asparaginase, L-asparagine amidohydrolase,Elspar, L-Asnase	L-ASP, Lcf-ASP	MK-965, Re-82-TAD-15
mercaptopurine	antimetabolite	6 thiohypoxanthine, 6 thiopurine, 6-mercaptopurine, 6-mercaptopurine monohydrate, 6-purinethiol, 6-thiopurine, 6-thioxopurine, Azathiopurine, Leupurin, Mercapurin, Mern, Purimethol, Purinethol, Purixan	6-MP, MP	BW 57-323H, U-4748, WR-2785
bortezomib	proteasomeInhibitor	PS-341, VELCADE		LDP 341, MLN341, PS-341
temozolomide	alkylatingAgent	Methazolastone, Temodar	TMZ	CCRG-81045, M & B 39831, RP-46161, SCH 52365
pegaspargase	enzyme	L-asparaginase with polyethylene glycol, PEG-asparaginase, PEG-L-asparaginase, PEG-L-asparaginase(K-H), polyethylene glycol-L-asparaginase,Oncaspar	PEG-ASP, PEGLA	

fluorouracil	antimetabolite	5-fluorouracil injection, 5-Fluracil, fluouracil, Fluracil,	5-FU injection, FU	Ro-2-9757
carmustine	alkylatingAgent	bis(chloroethyl) nitrosourea, bis-chloronitrosourea, carmustin,Becenum, BiCNU, Carmubris	BCNU	FDA 0345, SK 27702, SRI 1720, WR-139021
oxaliplatin	platinum	Ai Heng, Aiheng, diaminocyclohexane oxalatoplatinum, oxalatoplatin, oxalatoplatinum, oxaliplatine, Eloxatin	1-OHP, L-OHP	JM-83, RP-54780, SR-96669
lapatinib	tyrosineKinaseInhibitor	lapatinib ditosylate, Tykerb		GSK572016, GW2016, GW-572016
selumetinib	tyrosineKinaseInhibitor			ARRY-142886, AZD6244
mitoxantrone	anthracycline	mitoxantrone hydrochloride,dihydroxyanthracenedione, dihydroxyanthracenedione dihydrochloride, mitoxantrone dihydrochloride, mitoxantrone HCl, mitozantrone,	DHAD, DHAQ	CL 232315
bevacizumab	monoclonalAB	anti-VEGF humanized monoclonal antibody, anti-VEGF monoclonal antibody, anti-VEGF rhuMAb, bevacizumab biosimilar BEVZ92, bevacizumab biosimilar BI 695502, bevacizumab biosimilar CBT 124, bevacizumab biosimilar FKB238, bevacizumab biosimilar PF-06439535, immunoglobulin G1 (human-mouse monoclonal rhuMab-VEGF gamma-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMab-VEGF light chain, dimer recombinant humanized anti-VEGF monoclonal antibody, rhuMAb VEGF, Avastin, Mvasi	rhuMAb VEGF, rhuMab-VEGF	

hydrocortisone	steroid	Barseb-HC, Cortifan, cortisol, Domolene, Komed-HC,Aeroseb-HC, Barseb HC, Cetacort, Cort-Dome, Cortef, Cortenema, Cortispray, Cortril, Dermacort, Domolene-HC, Eldecort, Hydrocortone, Hytone, Komed HC, Nutracort, Proctocort, Rectoid	HC	
gemcitabine	antimetabolite	gemcitabine hydrochloride,	dFdCyd	
irinotecan	topoisomeraseInhibitor	irinotecan hydrochloride, camptothecin-11, irinotecan, irinotecan HCl, Camptosar	CPT-11, U-101440E	
azacitidine	antimetabolite	5-AC, 5-azacytidine, azacytidine, ladakamycin, Mylosar, Vidaza	5-AC, 5-AZC, AZA-CR	U-18496
alvocidib	kinaseInhibitor	Afinitor, Zortress	RAD001	
prednisolone	steroid	delta(1)hydrocortisone, delta1-dehydro-hydrocortisone, deltahydrocortisone, metacortandralone, Cortalone, Delta-Cortef, Hydeltra, Hydeltrasol, Meti-derm, Prelone	PRDL	
octreotide	hormone	octreotide acetate, Longastatin, Sandostatin, Sandostatin Lar Depot,		SMS 201-995
octreotide pamoate	hormone	ctreotide pamoate LAR(SMS 201-995), OP LAR, OncoLAR, Sandostatin pamoate, Sandostatin pamoate LAR		SMS 201-995 pa, SMS 201-995 pa LAR
vorinostat	statin	suberoylanilide hydroxamic acid, Zolinza	SAHA	L-001079038, MSK390
idarubicin	histoneDecetylaseInhibitor	idarubicin hydrochloride, 4-demethoxydaunomycin, 4-demethoxydaunorubicin, DMDR, idarubicin HCl, Idamycin	4-DMDR, IDA	IMI-30, SC-33428
dacomitinib	tyrosineKinaseInhibitor	EGFR inhibitor PF-00299804,		PF-00299804, PF-00299804-03
thiotepa	alkylatingAgent	thiofosfamide, thiophosphamide, thiophosphoramide, triethylene thiophosphoramide	TSPA	WR-45312
decitabine	hypomethylatingAgent	5-aza-dCyd, deoxyazacytidine, dezocitidine, Dacogen	5AZA, DAC	
erlotinib	tyrosineKinaseInhibitor	Tarceva		CP-358,774, CP358774, OSI774, OSI-774
lenalidomide	immunomodulatoryAgent	IMiD-1, Revlimid		CC-5013, CDC 501
gemtuzumab ozogamicin	monoclonalAB	gemtuzumab ozogamicin, Calicheamicin-Conjugated Humanized Anti-CD33 Monoclonal Antibody hP67.6-Calicheamicin, Mylotarg		CDP-771, CMA-676, WAY-CMA-676

pemetrexed	antimetabolite	pemetrexed disodium, multitargeted antifolate, Alimta	MTA	LY231514
topotecan	topoisomeraseInhibitor	liposomal topotecan hydrochloride, topotecan hydrochloride liposomes, Brakiva		
pomalidomide	immunomodulatoryAgent	Pomalyst		CC-4047
thymocyte	antithymocyte	anti-thymocyte globulin, lymphocyte immune globulin, ATGAM, Thymoglobulin	ATG	
capecitabine	antimetabolite	Xeloda	CAPE	Ro 09-1978/000
imatinib	tyrosineKinaseInhibitor	imatinib mesylate, Gleevec		CGP 57148, CGP57148B, STI-571
nilotinib	tyrosineKinaseInhibitor	Tasigna		AMN 107
belinostat	histoneDecetylaseInhibitor	Beleodaq		PXD 101, PXD101
thioguanine	antimetabolite	tioguanin, tioguanine, Tabloid	6-TG, TG	BW 5071, Wellcome, U3B, WR-1141, X 27
zibotentan	other			ZD4054
ipilimumab	monoclonalAB	anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody, MOAB CTLA-4, monoclonal antibody CTLA-4, Yervoy	MDX-CTLA-4	BMS-734016, MDX-010
dacarbazine	alkylatingAgent	Biocarbazine, Dacarbazina, Dacarbazina Almirall, Dacarbazine - DTIC, Dakarbazin, Dimethyl (triazeno) imidazolecarboxamide, Dimethyl Triazeno Imidazol Carboxamide, Dimethyl Triazeno Imidazole Carboxamide, Imidazole Carboxamide, Imidazole Carboxamide Dimethyltriazeno, DTIC-Dome	DIC, DTIC	WR-139007
ganetespib	other	Hsp90 inhibitor STA-9090		STA-9090
temsirolimus	mTORInhibitor	cell cycle inhibitor 779, rapamycin analog CCI-779, Torisel		CCI-779
gefitinib	tyrosineKinaseInhibitor	Iressa		ZD 1839
paclitaxel albumin-stabilized nanoparticle formulation	plantAlkaloid	albumin-bound paclitaxel, Albumin-Stabilized Nanoparticle Paclitaxel, nab paclitaxel, nab-paclitaxel, nanoparticle albumin-bound paclitaxel, Nanoparticle Paclitaxel, protein-bound paclitaxel, Abraxane		ABI-007
eribulin	microtubuleInhibitor	halichrondrin B analog, Halaven		B1939 mesylate, E7389, ER-086526
cediranib	tyrosineKinaseInhibitor	AZD2171 maleate, Recentin		AZD2171
entinostat	histoneDecetylaseInhibitor	HDAC inhibitor		
lomustine	alkylatingAgent	Lomustinum, Gleostine	CCNU	RB-1509, WR-139017
thalidomide	immunomodulatoryAgent	alpha-phthalimidoglutarimide, N-phthaloylglutamimide, N-phthalylglutamic acid imide, Thalomid	THAL	
arsenic trioxide	other	arsenic trioxide formulation ORH 2014, As2O3 formulation ORH 2014, oral arsenic trioxide formulation		ORH-2014
tretinoin	other	liposomal tretinoin, All-trans-retinoic acid liposomal, tretinoin liposomal, tretinoin liposome, tretinoinLF, Atragen	L-ATRA	AR-623

chlorambucil	alkylatingAgent	chlorambucilum, chloraminophen, Chlorbutin, chlorbutine, chlorbutinum, chloroambucil, chlorobutin, chlorobutine, Leukersan, Leukoran, Lympholysin, phenylbutyric acid nitrogen mustard, Ambochlorin, Amoclorin, Leukeran, Linfolizin	CHL, CLB	CB-1348, WR-139013
afimoxifene	hormoneInhibitor	4-Hydroxy-Tamoxifen		
tamoxifen	hormoneInhibitor	tamoxifen citrate, tamoxifeni citras, Nolvadex	TAM	ICI 46,474, ICI-46474
trabectedin	alkylatingAgent	ecteinascidin, Yondelis	ET 743	
cabozantinib	tyrosineKinaseInhibitor	cabozantinib-s-malate, Cabometyx, Cometriq		BMS-907351, XL 184
ramucirumab	monoclonalAB	anti-VEGFR-2 fully human monoclonal antibody IMC-1121B, Cyramza		IMC-1121B, LY3009806
cabazitaxel	taxane	taxoid XRP6258, Jevtana		RPR-116258A, XRP6258
nivolumab	monoclonalAB	anti-PD-1 human monoclonal antibody MDX-1106, Opdivo, Opdivo Injection	NIVO	BMS-936558, MDX-1106, ONO-4538
romidepsin	histoneDecetylaseInhibitor	depsipeptide, Istodax		FK228, FR901228, NSC 630176
amifostine	other	amifostine trihydrate, aminopropylaminoethylthiophosphoric acid trihydrate, ethiofos, gammaphos, Ethyol	APAETP	WR 2721, WR2721, WR-2721, YM-08310
sunitinib	tyrosineKinaseInhibitor	sunitinib malate, Sutent	SU11248	SU011248, SU011248, SU11248
panitumumab	monoclonalAB	clone E7.6.3, monoclonal antibody ABX-EGF, Vectibix	MOAB ABX-EGF	ABX-EGF
pazopanib	tyrosineKinaseInhibitor	pazopanib hydrochloride, Votrient		GW786034B
thioplex	alkylatingAgent	thiotepa, thiofosfamide, thiophosphamide, thiophosphoramide, triethylene thiophosphoramide	TSPA	WR 45312
alemtuzumab	monoclonalAB	anti-CD52 monoclonal antibody, Campath-1H, Monoclonal Antibody Campath-1H, Monoclonal Antibody CD52, Campath	MoAb CD52	
muromonab	monoclonalAB	muromonab-CD3, Anti-CD3 monoclonal antibody OKT3, MOAB OKT3, monoclonal antibody OKT3, OKT3, Orthoclone OKT3	MOAB OKT3	
ofatumumab	monoclonalAB	Arzerra		2F2, GSK1841157
pravastatin*	statin	pravastatin sodium, Pravachol	PRAV	
		*pravastatin sodium has potential antineoplastic activities		

Appendix B. Curriculum Vitae

Christina Eldredge, MD, MSMI

HOME ADDRESS:
17230 Emerald Chase Drive
Tampa, Florida 33647
PHONE: 847-909-6320
EMAIL: work**:** celdredge2@usf.edu
CITIZENSHIP: U.S.A

EDUCATION:

9/1988 – 5/1992 – B.S., Biology, University of Miami Biology, Coral Gables, FL

7/1992 - 6/1996 – M.D., University of Miami School of Medicine, Miami, FL

9/2008 – 2/2013 **–** MSMI, Medical College of Wisconsin/Milwaukee School of Engineering, Milwaukee, WI

1/2013 – 5/2020 – Biomedical and Health Informatics Doctorate Program, University of Wisconsin-Milwaukee, Milwaukee, WI

POSTGRADUATE TRAINING AND FELLOWSHIP APPOINTMENTS:

7/1996 - 6/1999 - Medical College of Wisconsin, Columbia Family Practice Residency Program, Milwaukee, WI

6/2010 - 5/2013- Academic Fellowship in Primary Care Research, Medical College of Wisconsin, Milwaukee, WI

9/2018-11/2018- NSF I-Corps Fellow, University of South Florida, Tampa, FL

MILITARY SERVICE:

7/1999 – 12/2003 – Family Medicine Physician, Lieutenant Commander, Medical Corps, U.S. Naval Hospital Great Lakes, Great Lakes, IL

FACULTY APPOINTMENTS:

6/2010 – 5/2013 **–** Fellow/Instructor**,** Academic Fellowship in Primary Care Research, Department of Family and Community Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

6/2013-5/2015- Clinical Instructor, Department of Family and Community Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

10/2014-12/2018-Adjunct Assistant Professor, University of Wisconsin-Milwaukee, Department of Health Informatics and Administration, Milwaukee, Wisconsin

1/2017-7/2017-Adjunct Instructor, University of South Florida, College of Arts & Sciences, School of Information, Tampa, Florida

8/2017-present-Visiting Instructor, University of South Florida, College of Arts & Sciences, School of Information, Tampa, Florida

3/2019-present-Adjunct Professor, Department of Molecular Medicine, Morsani College of Medicine, University of South Florida, Tampa, Florida

SPECIALTY BOARD AND CERTIFICATIONS:

Board Certified		Issue Date	Expiration
American Board of Family Medicine		1999	12/31/2025
Licensure	Number	Issue Date	Expiration
Wisconsin License	39039	1997	10/31/2021
Licensure	Number	Issue Date	Expiration
Florida License	ME 136748	2018	01/31/2022

MEMBERSHIPS IN HONORARY AND PROFESSIONAL SOCIETIES

2011 – 2013	Wisconsin Public Health Association
1994 – Present	Academy of Family Physicians
1995 – Present	Alpha Omega Alpha National Medical Honor Society
2011 – Present	American Medical Informatics Association (AMIA)
2018 – Present	Health Information and Management Systems Society (HIMSS)

AWARDS AND HONORS:

1994 University of Miami School of Medicine CIBA Award for Community Service
1995 Alpha Omega Alpha National Honor Medical Society (Officer 1995-1996)
2003 Navy and Marine Corps Achievement Medal for superior performance as one of three physicians to initiate the Family Practice Clinic at Naval Hospital Great Lakes
2012 Outstanding Medical Student Teacher Award from the Medical College of Wisconsin for Medical Interviewing

EDITORSHIPS/EDITORIAL BOARDS/JOURNAL REVIEWS:

Journal Review

2011-2015	Journal of School Health
2014-present	Wisconsin Medical Journal
2014-present	American Medical Informatics Association

INTERNATIONAL ELECTED/APPOINTED LEADERSHIP AND COMMITTEE POSITIONS:

10/2011 Track Co-Chair, ISCRAM, International Conference on Information Systems for Crisis Response and Management, Healthcare Crisis Management Systems Track

LOCAL/REGIONAL APPOINTED LEADERSHIP AND COMMITTEE POSITIONS:

1999 – 2002 Peer Review Coordinator, Family Practice Department, U.S. Naval Hospital Great Lakes, Great Lakes, IL

2001 – 2003 Member, Naval Dental and Biomedical Research Institutional Review Board, US Great Lakes Naval Base, Great Lakes, IL

2012 – 2015 Member, Archdiocese of Milwaukee Office for Schools Health and Wellness Steering Committee

2012 – 2015 St. Anthony School's Padre Pio Clinic Board of Directors Advisory Board (IAB)

2020-present Member, Information Day Planning Committee, iSchool, USF

NATIONAL APPOINTED LEADERSHIP AND COMMITTEE POSITIONS:

2015 Member, Multidisciplinary Anaphylaxis Advisory Board for Mylan Specialties, the maker of EpiPen®, April 17-18, 2015 in Canonsburg, PA

2015 University of Wisconsin-Milwaukee Representative, Academic Forum for the American Medical Informatics Association (AMIA). Participated at the national level in health informatics curriculum development.

2015-2019 Member, AMIA Health Informatics Accreditation Committee

2019-present Member, HIMSS Professional Development Committee

2020-present Member, AMIA Educational Committee

RESEARCH GRANTS/AWARDS/CONTRACTS/PROJECTS:

Peer Review

Title: NSF 14-547 PI: Paul Sandberg 04/01/2015 to 03/31/2019 Funding: $296, 435 INNOVATION CORPS (I-CORPS) SITES PROGRAM
Source: NSF
Role: I-Corps Fellow
Dates: Fall 2018

Title: Advancing Community-Partnerships for Translational Research: Scientific Citizens and Citizen Scientists
Source: Advancing a Healthier Wisconsin Endowment
Role: Faculty
Dates: 7/1/2010 – 6/30/2015
Direct Funds: $1,659,180

Title: Healthier Obstetrical Outcomes through Enrichment Activities and Community Engagement
Source: HWPP
Role: Co-Investigator
Dates: 1/1/2014-12/31/2015
Requested Funds: approx. $200,000

Title: Teleophthalmology to Improve Eye Health among Latinos (TIEHL): UCC-MCW-Marquette Collaboration
Source: HWPP
Role: Co-Investigator
Dates: 1/1/2014-6/30/2015
Requested Funds: approx. $200,000

Title: mPeer: Mobile Detection of High Risk Behavior in Veterans - A Sociotechnical Systems Approach
Source: Clinical and Translational Science Institute (CTSI)
Role: Co-investigator
Dates: 3/1/2013 - 11/1/2013
Direct Funds: $50,000 over 1 year

INVITED LECTURES/WORKSHOPS/PRESENTATIONS:

Speaker, "Applied Health Informatics Master's Level Education: A Discussion of Core Competencies", HIMSS20 Lightening Session, occurring March 12, 2020.

Keynote Speaker, "Connected Health: How your smartphone can manage your health", Information Day, University of South Florida School of Information
April 25, 2018.

Pediatric Food Allergy Management in the Community. CME Presentation. The Medical College of Wisconsin Department of Family and Community Medicine's 45nd Annual Winter Refresher Course for Family Medicine. Waukesha, WI, January 30, 2015.
Guest Lecturer, Translational Science and Translational Biomedical Informatics, Milwaukee School of Engineering Biomolecular Engineering (BioE) Program Seminar Course, January 13th, 2015

2014 Catholic Educators Convention, *Leading the Learning*
Presented: Food Allergy Update
Frontier Airlines Center, Milwaukee, October 10th, 2014.
Guest Lecturer, Clinical Research Informatics Case Presentation, Milwaukee School of Engineering Medical Informatics Case Study Course: September 19th, 2013, MSOE, Milwaukee, WI, September 15th, 2014, MSOE, Milwaukee, WI, October 22nd, 2015, MSOE, Milwaukee, WI

mHealth: Using Mobile Technology to Connect with Your Patient. The Medical College of Wisconsin Department of Family and Community Medicine's 44nd Annual Winter Refresher Course for Family Medicine. Waukesha, WI. February 5th, 2014.
2012 Catholic Educators Convention, *Catholic Schools: A Commitment to Excellence*
Presented: Managing Food Allergies in the Classroom
Frontier Airlines Center, Milwaukee, October 12th, 2012.
Facilitator, Community Health Informatics Workshop, Information Technology Resources for Research Breakout Session, University of Wisconsin-Milwaukee School of Continuing Education Conference Center, Tuesday October 2, 2012, Milwaukee, WI.

Pediatric Food Allergy: School-Based Management. CME Presentation. The Medical College of Wisconsin Department of Family and Community Medicine's 42nd Annual Winter Refresher Course for Family Medicine. Waukesha, WI. February 3rd, 2012.

PEER REVIEWED PRESENTATIONS

Poster presentations

Local

Golam M. Tanimul Ahsan, **Christina Eldredge, MD MS**; Brenda White, EdS; Zeno Franco, PhD; Sheikh I. Ahamed, PhD. mHealth for School Emergency Preparedness. Clinical & Translational Science Institute of Southeast Wisconsin's Community Health Informatics Workshop, Milwaukee, WI, May 30, 2013.

Eldredge CE, Patterson L, Schellhase K. Implementation of Food Allergy Management Policies in Private Schools. 20th Annual Department of Family and Community Medicine Research Forum. Medical College of Wisconsin, Milwaukee, WI, May 23rd, 2011.

Regional

Patterson L, Morzinski J, **Eldredge CE**. Using Veterans as Peer-Group Health Workers to Improve Hypertension Awareness and Management. 2011 Wisconsin Public Health Association and Wisconsin Association of Local Health Departments and Boards Annual Conference, "Healthiest State in One Generation". Appleton, WI, May 24-26, 2011.

National

Eldredge C., Andrews J.E., Zolnoori M., Patrick T., Gallagher J., Lam C. and J. Luo. Challenges to a Data Driven Approach to Population Level Analysis of Hypersensitivity Events in Cancer Clinical Trials. Poster presented at the AMIA Annual Symposium, November 19, 2019, Washington, D.C.

Lam C., **Eldredge C.,** Andrews J., Perkins R. Challenges to Data Abstraction to Characterize Contrast Media Reactions and Identify Potential Risk Factors in a Cancer Patient Population. Poster presented at the AMIA Annual Symposium, November 19, 2019, Washington, D.C.

Lam C., **Eldredge C.,** Andrews J.E. and Perkins R. Adverse Contrast Media Event Documentation: A Cancer Center Perspective. Poster presented at the AMIA Clinical Informatics Conference, April 30 – May 2, 2019, Atlanta, GA.

Andrews J.E., **Eldredge C**, and Cooperman C. Building an Institute for Health Sciences Information (Ihsi): Connecting Education, Industry, and Research. Accepted to the AMIA InSpire 2017: Developing the Health Informatics Workforce of the Future conference, La Jolla, CA, June 6-8, 2017.

Joel Gallagher; Robert Rivera; Asriani Chiu; Tanvir Roushan; Golam Mushih Tanimul Ahsan; Cheng Wen; **Christina Eldredge**; Sheikh Iqbal Ahamed. "The Use of a mHealth Decision Tree Support Program for Epinephrine Auto-injector (EAI) Administration Training of Adolescents" *AMIA 2016 Annual Symposium Conference Proceedings*, Washington DC, Nov. 15, 2016.

Eldredge, Christina; Ahsan, Golam Mushih Tanimul; Chiu, Asriani; White, Brenda; Atchison, Taylor; Patterson, Leslie; Ahamed, Sheikh Iqbal. "Pilot assessment of a caregiver decision support mobile health (mHealth) application for food allergy & anaphylaxis in the school environment." *AMIA 2014 Annual Symposium Conference Proceedings*, Washington DC, Nov. 15-19, 2014.

Christina **Eldredge**, MD MS; Golam M Tanimul Ahsan; Zeno Franco, PhD; Brenda White, Ed.S.; Asriani M. Chiu, MD; Leslie Patterson, PhD MS; Mohammad Arif Ul Alam; Sheikh Iqbal Ahamed, PhD. mHealth for School Food Allergy Emergency Preparedness. mHealth Summit. Washington D.C. December 2013.

Slawson J, **Eldredge CE**, Hughes J, Payne J, Olsen S, Leienger M. Benefits of a Patient Centered Medical Home for High Risk OB Care: A first year preliminary report. 5th Annual National CTSA Community Engagement Conference, "Methods, Metrics and outcomes: Evaluating the Success of Community Engaged Research", Bethesda, MD, August 23rd-24th, 2012.

Eldredge CE, Slawson J, Granados R, Payne J. Developing a Combined Research and QI Database from Community Based Practices with Different IT Systems. 4th Annual National CTSA Community Engagement Conference, "Using IT to Improve Community Health: How Health Care Reform Supports Innovation". Bethesda, MD, August 30th-31st, 2011.

Morzinski J., Patterson L., **Eldredge CE**. Teaching Community Health Workers to Train Peers About Hypertension: Outcomes & Implications. Society of Teachers of Family Medicine Spring Conference, New Orleans, LA, April 2011.

Educational Exhibits/Workshops

Zolnoori, M., Patrick, T. B., Fung, KW., Fontelo P., Faiola, A., Wu YS. S., Xu, K., Zhu, J., **Eldredge, C. E.** Development of an Adverse Drug Reaction Corpus from Consumer Health Posts. *Workshop: American Medical Informatics Association, Annual Symposium*, Washington, DC., *November, 2017*. http://ceur-ws.org/Vol-1996/paper3.pdf

Lam CA, **Eldredge C**, Taylor B, Ahmed N, Kahn C. Feasibility of a Generalized Informatics Framework for Cohort Identification, Hypothesis Generation, and Retrospective Data Analysis for Radiology Research - Educational Exhibit. Chicago, IL, Radiological Society of North American (RSNA) Meeting 2013.

National Oral Presentations

Zolnoori M., Ngufor C., Faiola A., **Eldredge C.,** Luo J., Sunghwan S., Balls-Berry J.E., Tafi A.P., Shah N.D., Patrick T.B. Identifying Factors Affecting Drug Discontinuation in Patients with Depression: Text Analysis of Patient Drug Review Post. Podium Abstract presented at the AMIA Annual Symposium, November 19, 2019, Washington, D.C.

Eldredge C, Singavi A, Lam C, Gallagher J and Luo J. Big Data Analysis of Drug Induced Hypersensitivity and Anaphylaxis Reactions in Clinical Cancer Trails. AAAAI/WAO, Orlando, FL, March 3, 2018. *Journal of Allergy and Clinical Immunology*, Vol 141, Issue 2, Supplement, Page AB87.

Lam CA, **Eldredge C**, Sawlani R, Bushee G, Taylor B, Kahn C. *Assessing the Validity of Contrast Induced Nephropathy Using the i2b2 Informatics Framework: A Retrospective 3-year Electronic Medical Record Review. Oral Paper Presentation.* Chicago, IL, RSNA 2014.

MEDICAL COLLEGE TEACHING ACTIVITIES:

Community/Lay Public
2011 Archdiocese of Milwaukee School Staff Medication Training Day

Medical Student Education
2012-2014 Instructor, M1 Foundations of Clinical Medicine course
2011-2014 Instructor, CHCR Family Medicine Clerkship
2011-2012 Instructor, Medical Interviewing
2010-2013 Facilitator, Medical Student Intercessions
2010-2013 Facilitator, Urban and Community Health Pathway

STUDENTS, FACULTY, RESIDENTS AND CLINICAL/RESEARCH FELLOWS MENTORED:

Medical Students:

6/2012 – 9/2012 Medical College of Wisconsin, M2 Summer Research Internship Student
9/2011 – 5/2014 Medical College of Wisconsin, Urban and Community Pathway Student
9/2012 – 5/2018 Medical College of Wisconsin, Quality Improvement Pathway Students

Masters Students and Fellows:

2014 – 2015	Marquette Computer Science Student, member of Masters' Thesis Committee
2014 – 2017	Medical College of Wisconsin Allergy and Immunology Fellow, member of his Scholarly Oversight Committee and mentor for a mobile health project
2016 - 2018	Medical College of Wisconsin, Hematology and Oncology Fellow, mentor in Health Informatics

PUBLICATIONS:

Maryam Zolnoori; Kin Wah Fung; Timothy Patrick; Paul Fontelo; Hadi Kharrazi; Anthony Faiola; Yi Shuan Shirley Wu; **Christina E. Eldredge**; Jake Luo; Mike Conway; Jiaxi Zhu; Soo Kyung Park; Kelly Xu; Hamideh Moayyed**.** (2019, March 21). The PsyTAR Dataset: From Patients Generated Narratives to a Corpus of Adverse Drug Events and effectiveness of Psychiatric Medications. *Data in brief*. 24:103838. PMID: 31065579

Maryam Zolnoori; Kin Wah Fung; Timothy Patrick; Paul Fontelo; Hadi Kharrazi; Anthony Faiola; Yi Shuan Shirley Wu; **Christina E. Eldredge**; Jake Luo; Mike Conway; Jiaxi Zhu; Soo Kyung Park; Kelly Xu; Hamideh Moayyed; Somaieh Goudarzvand. (2019, Jan 3) A Systematic Approach for Developing a Corpus of Patient Reported Adverse Drug Events: A Case Study for SSRI and SNRI Medications. *Journal of Biomedical Informatics*. PMID: 30611893

Annette L Valenta, Eta S Berner, Suzanne A Boren, Gloria J Deckard, **Christina Eldredge**, Douglas B Fridsma, Cynthia Gadd, Yang Gong, Todd Johnson, Josette Jones, E LaVerne Manos, Kirk T Phillips, Nancy K Roderer, Douglas Rosendale, Anne M Turner, Guenter Tusch, Jeffrey J Williamson, Stephen B Johnson. (2018, Dec. 1) AMIA Board White Paper: AMIA 2017 core competencies for applied health informatics education at the master's degree level. *Journal of the American Medical Informatics Association*, 25 (12): 1657-1668. PMID: 30371862

Gallagher JL, Rivera RD, Van Shepard K, Roushan T, Ahsan G, Ahamed SI, Chiu A, Jurken M, Simpson PM, Nugent M, Gobin KS, Wen CKF, and **Eldredge CE**. (2018, Jul 3). Life-Threatening Allergies: Using a Patient-Engaged Approach. *Telemedicine Journal and e-Health.* PMID: 29969372

Luo J, **Eldredge C**, Cho CC, Cisler RA. (2016) Population Analysis of Adverse Events in Different Age Groups Using Big Clinical Trials Data. *JMIR Med Inform*, 4(4): e30. PMID: 27751983

Jackson J, Cogbill E, Santana-Davila R, **Eldredge C**, William C, Gradell A, Sehgal N, Kuester J. (2015, Jul 14) A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. *PLOS ONE*, 10(7): E0130733. PMID: 26172390

Eldredge C, Patterson L, White B, Schellhase K. (2014, Aug) Assessing the Readiness of a School System to Adopt Food Allergy Management Guidelines. *Wisconsin Medical Journal,* 113 (4); 155-161. PMID: 25211803

Bradford L, **Eldredge CE**, Morzinski, JA. (2013, Feb) Training community-engaged researchers. *Academic Medicine*, 88(2):154. PMID: 23361025

Eldredge CE and Schellhase K. (2012, Jul 1) School-Based Management of Food Allergies in Children. *American Family Physician*, 86(1), 16-18. PMID: 22962908

Marriott LK, Nelson DA, Allen S, Allen, S. Calhoun, K. **Eldredge CE**. Kimminau KS. Lucero RJ. Pineda-Reyes F. Rumala BB, Varanasi, AP, Wasser, JS, Shannon J. (2012, Feb. 1) Using health information technology to engage communities in health, education, and research. *Science Translational Medicine*, 4(119), 119mr111. PMID: 22301550

Kahn CE, Jr., Kalpathy-Cramer J, Lam CA, **Eldredge CE**. Accurate Determination of Imaging Modality using an Ensemble of Text- and Image-Based Classifiers. (2011, Jul 6) *Journal of Digital Imaging*, 25(1), 37-42. PMID: 21748413

Book Chapter

Andrews, J. E., Johnson, J.D., & Eldredge, C. (2019). The evolving roles of consumers. In R. Richesson & J.E. Andrews (Eds). Clinical Research Informatics. Springer-Verlag: London 2nd ed.