Consolidated Health Informatics

Standards Adoption Recommendation

Medications Report Summary

Subdomain recommendations described in this report:

- Special Populations
- Drug Classifications

Subdomain recommendations described in separate reports:

- Clinical drug (med_clindrug_public_full.doc)
- Manufactured dosage form (med_dose_public_full.doc)
- Medication Ingredient (med_ingred_public_full.doc)
- Package (medpkg_public_full.doc)
- Product (medprod_public_full.doc)
- Structured Product Label (medSPL_public_full.doc)

Summary

Domain: Medications

Sub-Domain: Special Populations

Standards Adoption Recommendation:
Health Level Seven® (HL7®) Version 2.4

SCOPE
Sub-groups of the population using medications for the treatment or prevention of medical conditions can demonstrate difference in the safety and effectiveness of these products. (Gender, Age, Race/Ethnicity)

RECOMMENDATION
HL7® Version 2.4 gender, race & ethnicity codes—which covers the OMB guidelines as well as a more granular characterization hierarchically grouped according to the OMB categories. (Consistent with CHI demographics standards)

OWNERSHIP
Health Level Seven® (HL®7) holds the copyright, www.hl7.org

APPROVALS AND ACCREDITATIONS
HL7® is an ANSI-accredited Standards Developing Organization. This standard has been approved by full organizational ballot voting.

ACQUISITION AND COST
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Summary

Domain: Medications

Sub-Domain: Drug Classifications

Standards Adoption Recommendation:
National Drug File Reference Terminology (NDF-RT)
(for Physiologic Effect & Mechanism of Action)

SCOPE
One of the desired qualities of a standardized medication terminology is the inclusion of hierarchical structures to categorize each medication, such as: mechanism of action, physiologic effects, intended therapeutic use, chemical structures, pharmacological properties, and FDA approved indications.

RECOMMENDATION
The National Drug File Reference Terminology (NDF-RT) classification scheme for the areas of Physiologic Effect and Mechanism of Action.

OWNERSHIP
The Veterans Administration developed the NDF-RT.

APPROVALS AND ACCREDITATIONS

ACQUISITION AND COST
May be obtained from the VA. Also available from the National Cancer Institute at http://nciterms.nci.nih.gov/NCIBrowser/Connect.do

REVISION HISTORY

DATE	VERSION	COMMENT
2/17/2004	Public Document	Final Recommendation
2/24/2006	1.1	Outdated ballot reference deleted

Summary of Recommendations

Subdomain	Recommendation	Status
Active Ingredient	FDA Ingredient & Unique Ingredient Identifier (UNII) codes	FDA work underway to make available in 2004
Clinical Drug	RxNORM	NLM work underway to release production version
Manufactured Dosage Form	FDA/CDER standards manual	Freely available now
Drug product	FDA's National Drug Codes(NDC)	Freely available now
Medication Package	FDA/CDER standards manual	Freely available now
Labeling Section Headers	LOINC® Clinical Structured Product Labeling (SPL)	Being balloted through HL7 for trial use
Special Populations	HL7® Gender, Race and Ethnicity codes	Consistent with HL7® demographics standards already adopted
Drug Classifications	National Drug File Reference Terminology (NDF-RT) for specific uses	Adopted for mechanism of action and physiologic effect classifications
Adverse Events	*Deferred*	
Dosage & Administration	*Deferred*	
Indications	*Deferred*	
Contraindications	*Deferred*	
Pharmacokinetics & Pharmacodynamics	*Deferred*	

Overview of Rationale

The CHI Medications group reviewed a large number of potential candidate terminologies for representing drug product information. One criterion, respect for existing regulatory authority, bears special mention. The FDA is the United States regulatory authority for approving the safe and effective use of drug products in the US, and is collaboratively responsible for national and international harmonization of a number of drug-related issues. Product information, including the naming and coding of medications and their associated products, packaging, and other descriptive information is an FDA regulatory responsibility. The CHI medications group recommendations reflect this authority. While a number of medication-related terminologies include FDA determined and sanctioned names, selecting non-FDA terminologies as government standards would effectively usurp FDA's legal role. The CHI recommended standards that are not solely administered by FDA, such as LOINC® names for label section headers, have significant FDA input nonetheless. In addition, the CHI standards

consensus process calls for approval by FDA (or any other federal agency with regulatory authority) prior to adoption or use of the standard. In essence, the consensus process used by CHI addresses the need for approval by all affected federal agencies. In addition, the Department of Veterans Affairs (VA) has confirmed their intent to continue participation in CHI as a partner, including review and approval of all subsequent NDF-RT releases by FDA.

Required SNOMED CT® Statement

SNOMED CT® was not among the terminologies selected by the medications group for a number of reasons. First, the FDA is the legal regulatory authority for medication-related terminology in the U.S. As described above, selecting SNOMED CT® would conflict with FDA's regulatory mission and authority. Lesser, but still true considerations follow. The government license specifically excludes a portion of SNOMED CT® related to medications. Secondly, SNOMED CT®'s medication terminology is a relatively less developed component of the product. The FDA internal evaluations of SNOMED®'s coverage of drug names of substances involved in drug interactions found additional large content gaps. Thirdly, SNOMED CT®'s update frequency is measured in months. This interval is far too infrequent given the rate of change in certain components medication-related terminology. Finally, all CHI medication group selections are freely available at no additional cost, and impose no additional burdens on the user.

Introduction

The Consolidated Health Informatics (CHI) initiative will establish a portfolio of existing clinical vocabularies and messaging standards enabling federal agencies to build interoperable federal health data systems. This commonality will enable all federal agencies to "speak the same language" and share that information without the high cost of translation or data re-entry. Federal agencies could then pursue projects meeting their individual business needs aimed at initiatives such as sharing electronic medical records and electronic patient identification. CHI standards will work in conjunction with the Health Insurance Portability and Accountability Act (HIPAA) transaction records and code sets and HIPAA security and privacy provisions.

The charge to the medications working group was to identify and make recommendations for adoption of terminology standards for the exchange of drug product information. This charge was quite broad in scope, representing standards for information ranging from the description of drugs, the acts of prescribing, administration or record keeping for medicinal products to the clinical information necessary for the safe and effective use of drugs.

Recommendations for standard code sets and terminology for delivery of health care services and billing of medications are available at standards development organizations after being developed for HIPAA initiatives. The scope of this initiative was refined to focus upon the identification of terminology and standards necessary for clinical support and decision making, resulting in recommendations for adoption of terminology, code sets and other interoperability standards for drug product information.

Information critical for the support of clinical use of medicinal products or drugs was identified as the refined focus of the initiative.

Medications Group Timeline

Medications Group lead selection notification 1/22/03.
Medications team roster and contact information finalized 2/27/03
Kick off call, scope discussion, initial assignments 3/11/03
Preliminary analysis discussion and sub-domain selection 3/20/03
Selection criteria discussion 4/10/03
Detailed Analysis – June 2003
Report – April-June 2003

Medication Group Members

CDC: Dan Budnitz
Bill Trick
DoD Dave Hardy

Nancy Orvis

FDA Bill Hess
Kathy Hollinger
Randy Levin

IHS Carlene.McIntyre
NLM Stuart Nelson
VA Steve Brown

Drug Definition

Drugs are defined as those products intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, manifestations or symptoms of disease or alter structure/function of the body were considered the area of initial interest[1]. This definition encompasses products represented by a single molecular entity and more complex products such as biologicals, including vaccines. Generally, herbal supplements that do not make claims for disease conditions or their manifestations/symptoms are excluded from this regulatory-based definition of a drug.

Other related definitions:
21CFR314
(i)Drug substance. A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, specifications relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii)(a) Drug product. A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product); and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; the name and address of each manufacturer the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, specifications relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls,

[1] FD&C Act Section 503

methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

Uses of Medication Terminology within Represented Agencies

CDC

1. Surveillance (signal detection for bioterrorism, antibiotic use and resistance, treatment of reportable diseases)
2. Clinical care (vaccine administration, antibiotic prophylaxis)
3. Adverse event reporting (drugs, vaccines)
4. Research (case-mix adjustment, therapeutic mismatches for anti-infective therapy.)

DOD

1. Clinical care processes
2. Provider order entry (outpatient)
3. Pharmacy business processes
4. Inventory, and dispensing
5. Research
6. Clinical medication use practices
7. Management queries

FDA

1. Enhance availability of product information
    a. Improve consumer access to product information
    b. Enhance access to authentic labeling to ascertain product integrity
2. Research
    a. Evaluate or compare products for differences in subpopulation (gender, race/ethnicity, age) response and dosage regimens
    b. Evaluate drug-drug interactions
3. Medication Safety
    a. More accurate and timely updates of product information
    b. Enhancing access to product information for better prescribing decisions in clinical practice and dispensing
4. Institutional
    a. Improve access to product information for review and adverse event decision support
    b. Improve risk management by enhancing institutional knowledge base

Indian Health Service

The IHS needs standard terminology for medications at a local level between applications in order to conduct audits, for decision support, accurate third party billing for

medications, patient safety, and for continuity of care between facilities. At a national level, we need standard medication terminology for management analyses, quality of care assessments, billing and cost analyses, to obtain accurate measures for GPRA, HEDIS, Oryx, Healthy People 2010, and other outcomes analyses in an automated fashion. IHS needs to improve its ability to recognize and quickly respond to problems that impact the health of our patient populations.

NLM

1. Index the medical literature
2. Provide consumer health information via medlineplus.gov
3. Provide clinical research data via www.clinical trials.gov
4. Provide toxicology information via ToxNet
5. Provide chemical information via ChemIDplus
6. Provision of other specialized information services

VA

8. Clinical care processes
9. Provider order entry, alerting and decision support
10. Bar code medication administration
11. Pharmacy business processes
12. Inventory, and dispensing
13. Research
14. Clinical medication use practices
15. Management queries

Medication Subdomains – Scoped for Initial Analysis

1. Active Ingredient
2. Medication Component
3. Clinical Drug
4. Finished Dosage Form
5. Product
6. Package
7. Pharmacokinetics & Pharmacodynamics
8. Subpopulation definitions
9. Dosage Adjustments
10. Indications
11. Contraindications
12. Drug Classes
13. Medication Orders
14. Prescriptions

15. Supplies
16. Adverse Events
17. Labeling Section headers

Subdomain Definitions and Initial Analysis

1. Active Ingredient

Definition: An active ingredient is a substance responsible for the effects of a medication. Frequently, an active ingredient is a known chemical substance. Known chemical substances may be called by the base substance (e.g. propanolol), or by a base substance – salt combination (e.g. propanolol hydrocloride). In certain instances the structure of the ingredient is not known precisely. For example, beef gelatin is a complex molecular mixture defined by the process used to create it.

Options to Consider: United States Adopted Names (USAN), Chemical Abstracts Society (CAS) number, MolFile chemical structure representation and code; IUPAC chemical name.

Option Status: Mature, choice is possible

2. Drug Component

Definition: The drug component consists of an ingredient and strength. The Component Field can be repeated an arbitrary number of times until all the active components are named. An example of a drug component is “codeine phosphate 30 mg”

Options to Consider: RxNORM/NDF-RT. Drug Kb vendors may have similar representation. British Model.

Option Status: Moderate maturity, choice maybe possible. Selection will be included in clinical drug analysis

3. Clinical Drug

Definition: A clinical drug is defined by its active ingredients, strengths, and orderable dose forms. The concept is base on work from HL7®. The HL7® model was based on what a clinician might order, and what type of order might be sent to the pharmacy. The dose form is the form in which a drug is administered to a patient, as opposed to the form in which the manufacturer had supplied it. It is distinct from the choices the pharmacy might make in fulfilling that order.

Options to Consider: RxNORM/NDF-RT, Micromedix, Multum, First Databank, Medispan, British Model.

Option Status: Mature, choice is possible

4. Manufactured Dosage Form

Definition: A manufactured dosage form is the way of identifying the drug in its physical form. The following factors should be examined in determining dosage form, (1) physical appearance of the drug product, (2) physical form of the drug product prior to dispensing to the patient, (3) the way the product is administered, (4) frequency of dosing, and (5) how pharmacists and other health professionals might recognize and handle the product.

Options to Consider: 21 CFR and other FDA documents

Option Status: Mature, detailed analysis will be presented along with products.

5. Drug product and finished dosage form

Definition: A drug product is one or more finished dosage forms that contain one or more ingredients.

Options to Consider: 21 CFR 206.3; 21 CFR 314.3(b); 21 CFR 320.1(b); and 21 CFR 210.3(b)(4).

Option Status: Mature

6. Package

Definition: A drug package is, generally, any container or wrapping in which any drug is enclosed for use in the delivery or display of such commodities to retail purchasers. If no package is used, the container shall be deemed to be the package. It does not include: (a) Shipping containers or wrappings used solely for the transportation of any such commodity in bulk or in quantity to manufacturers, packers, processors, or wholesale or retail distributors; (b) Shipping containers or outer wrappings used by retailers to ship or deliver any such commodity to retail customers if such containers and wrappings bear no printed matter pertaining to any particular commodity; or (c) Containers subject to the provisions of the Act of August 3, 1912 (37 Stat. 250, as amended; 15 U.S.C. 231-233), the Act of March 4, 1915 (38 Stat. 1186, as amended; 15 U.S.C. 234-236), the Act of August 31, 1916 (39 Stat. 673, as amended; 15 U.S.C. 251-256), or the Act of May 21, 1928 (45 Stat. 635, as amended; 15 U.S.C. 257-257i). (d) Containers used for tray pack displays in retail establishments. (e) Transparent wrappers or containers which do not bear written, printed, or graphic matter obscuring the label information required by this part."

Options to Consider: 21 CFR 1.20; and 21 CFR 600.3.

Option Status: Mature

7. Special Populations/Sub-populations

Definition: Regulated drug product information is intended to be the comprehensive prescribing information for the safe and effective use of drugs. In product labeling considerations of differences in response in special populations is characterized in many parts of product labeling. There may be differences noted in dosage, contraindications, warning and other sections of drug product labeling. These sub-population differences described in labeling are based upon evidence provided by the product sponsor either from clinical studies or post-marketing adverse events.

Sub-groups of the population using medications for the treatment or prevention of medical conditions can demonstrate differences in the safety and effectiveness of these products. These differences may be attributable to intrinsic factors (e.g., genetic, clearance[2], disease condition), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Sub-populations that have demonstrated differences in response to drugs used to treat or prevent medical conditions include those grouped by age, race/ethnicity, sex and disease states or other physiologic impairment[3].

Differences in response to medical products have been observed in racially and ethnically distinct subgroups of the U.S. population. For example, in the United States, Whites[4] are more likely than persons of Asian and African heritage to have abnormally low levels of an important enzyme (CYP2D6) that metabolizes drugs belonging to a variety of therapeutic areas, such as antidepressants, antipsychotics, and beta blockers (Xie 2001). Additionally, after using some drugs in the psychotherapeutic class, slower enzyme metabolism (CYP2C19) has been observed in persons in the United States of Asian descent as compared to Whites and Blacks (Xie 2001). Other studies have shown that Blacks respond poorly to several classes of antihypertensive agents (beta blockers and angiotensin converting enzyme (ACE) inhibitors) (Exner 2001 and Yancy 2001). Racial differences in skin structure and physiology have been noted that can affect response to dermatological and topically applied products (Taylor 2002). Clinical trials have demonstrated lower responses to interferon-alpha used in the treatment of hepatitis C among Blacks when compared to other racial subgroups (McHutchison 2000 and Reddy 1999).

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[2] Clearance is a measure of drug or biologic elimination from the body.

[3] Food and Drug Administration (FDA), 1998, "Investigational New Drug Applications and New Drug Applications," Final Rule, *Federal Register*, Vol. 63 p. 6854, February 11, 1998.

[4] The terms used in this guidance to describe the various racial and ethnic groups are those used by OMB.

Similarly, gender differences in response can include prolongation of the QT interval and result in the development of a life-threatening cardiac arrhythmia. Women may also respond differently depending upon their reproductive status. Pregnant and nursing women taking medications represent another level of concern for the safety and effectiveness of medications. Differences in response to therapeutic products are observed between the very young and the aged. Neonates and infants metabolize drugs differently compared to adults, as the physiologic mechanisms for metabolism and elimination of drugs have not fully matured. Geriatric patients are often prescribed several medications concurrently and may react when these drugs cannot be effectively eliminated. Finally, sub-groups of the population having certain disease conditions, for example, hepatic or renal disease, can impair an individuals ability to metabolize or eliminate a medical product making them more susceptible to an overdose of the product.

Type of sub-domain and other information needed to assess sub-population differences in response to medical products:

A. Special populations characterized by Race/ethnicity

The characterization of Race and ethnicity that is defined here is pertinent to US populations.

Content: OMB Directive 15, 1997; FDA Guidance on the Collection of Race and Ethnicity Data in Clinical Trials (includes international participants)

Race & Ethnicity Code Options to Consider

Health Level Seven® –Offers OMB categories and more granular characterization hierarchically grouped according to the OMB categories. See below for current terminology/code sets. .

HL7® Race:

URL http://www.hl7.org/v3ballot/html/foundationdocuments/referencefiles/Race.htm
Advantage: Well structured, inclusion of hierarchical representation of international races.
Disadvantage: Classifications are socio-cultural in origin and not scientifically derived.

HL7® Ethnicity:

URL:
http://www.hl7.org/v3ballot/html/foundationdocuments/referencefiles/Ethnicity.htm
Advantage: Addresses national OMB requirements and offers more granular options based upon regional origin hierarchically linked to the alternative ethnicities.
Disadvantage: Very incomplete listing of ethnicity. Limited to Hispanic or Latino or not.

HL7® Native entity:
http://www.hl7.org/v3ballot/html/foundationdocuments/referencefiles/TribalEntityUS.htm
Advantage: Well constructed list of Native American entities.
Disadvantage: Not known

CDC – Detailed listing and codes for race and ethnicity:
Advantage: Extensive listing of Native American tribes. Hierarchical listing under OMB listed categories. Non-proprietary.
Disadvantage: Nationalities provided for international characterizations rather than racial or ethnic characterization. Code set available but not adopted by an SDO.
ISO
X12
FIPS Federal information processing standards
Numerous others may have been identified by Demographics group-
Note: CHI Demographics group may have identified additional resources.

Race & Ethnicity Option Status: Mature

B. ***Special populations characterized by Sex***

Content: General characterizations, Male, Female, Other, Unknown

Gender Code Options to Consider

Health Level Seven®
:
URL:
http://www.hl7.org/v3ballot/html/foundationdocuments/referencefiles/AdministrativeGender.htm
Advantage: Provides list of sex/gender.
Disadvantage: Does not address "other," or identify distinction between sex and gender.
Gender status:
http://www.hl7.org/v3ballot/html/foundationdocuments/referencefiles/GenderStatus.htm
ISO
X12
FIPS Federal information processing standards
Numerous others may have been identified by Demographics group

Gender Option Status: Mature

C. Special populations characterized by Age

Content for Age: Generally age may be represented by the days, month or years since Birth or may be classified based upon stage of life.

Options to Consider for Age: HL7® TS date, ISO age format

Age Option Status: Mature

Options to Consider for age classification –

FDA/International Conference on Harmonization on Age classifications
- Pediatric (0-16 years)
- Adult
- Geriatric (>65 years)

Or

- Neonate (0-1 month)
- Infant (1 month-2 years)
- Child (2-12 years)
- Adolescent (12-18 years)
- Adult (18-64 years)
- Geriatric (>65 years)

EMEA classification
- Preterm neonate
- Neonate (birth –27 days)
- Infant or toddler (28 days –2 years)
- Child (2-11 years)
- Adolescent (12-18 years)
- Adult (19-65 years)
- Elderly (>65 years)

Others
ISO
X12
FIPS Federal information processing standards
Numerous others may have been identified by Demographics group-
CHI Demographics group may have identified additional resources

Age Classification Option Status: Mature.

D. Special populations characterized by disease condition:

Content

Special populations may be represented by a disease or manifestations of a disease and terms that qualify the condition in some manner. Examples include renal impairment or hepatic failure. Disease modifier Code Sets/Terminology Examples may include severe,

moderate or mild. These terms may be in SNOMED® or other terminologies. Other disease classification systems may also be used, for example stage II breast cancer, to describe the disease or condition and these qualifiers may be available in terminologies.

Options to Consider: Problem (disease) Terminology:

SNOMED®
DSM-IV™
MeSH®
CPT®
Other(s)

Option Status: Information model to be developed. Care should be taken to ensure integration with medical problems. Work on information model is currently underway. Disease terminologies are mature in general; major open topic is their ability to represent special population defining content. Suggest revisiting topic in 1 year.

E. Other Special populations:

Content FDA has identified several special populations in regulations for which drug labeling must specify special conditions of use.

Options to Consider: Health Level Seven® Labeling Specification defines the areas, but not the underlying terminologies to be used in each area. Terminologies need to be evaluated and selected to cover the following areas:

Brief overview of potential candidates/what work has been done to date.

1. The FDA has recommended the standardized collection of race and ethnicity data in clinical trials in draft guidance. The guidance will be finalized in FY2004
2. The FDA has required that sponsors of medical products provide data on participants and differences in sub-population response to medical products in applications submitted for evaluations of safety and efficacy.

Status: This is a complex area that will require extensive information modeling and multiple terminologies to be developed. Work underway, revisit topic in 1 year

8. Dosage

Definition: Addresses dose and range of dosing for a user of the product. This also identifies drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in-vitro, as in a solution for intravenous administration. Labeling information regarding dosage also includes " the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of

dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules"

Status: To be developed. Work underway, revisit topic in 1 year. Status: Exploratory at this point in time.

Type of sub-domain information:

Strength
Dosage Form

Options to Consider:

Health Level 7®
http://www.hl7.org/v3ballot/html/foundationdocuments/referencefiles/OrderableDrugForm.htm

FDA Data Standards Manual: C-DRG-00201
Description. This standard provides for all drug dosage forms. The granularity of data often requires that more specific dosage form terms be stored in CDER's automated databases then is represented in its publications. These dosage form terms are available in databases that track approved drug products, but also for drug products such as those that have not been approved, investigational drug products, homeopathic drug products, and bulk drug products.

Work to date

FDA is collaborating with HL7® vocabulary group to develop a vocabulary for dosage.

Option Status: To be developed. Work underway, revisit topic in 1 year

9. Administration

Addresses the route of administration of a substance. Administration information in labels contains "specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities"

Type of sub-domain information:
Listing of routes that may be classified by method of administration.

Options to Consider:

Health Level 7®
http://www.hl7.org/v3ballot/html/foundationdocuments/referencefiles/RouteOfAdministration.htm

FDA Data Standards Manual: C-DRG-00301
Description. This standard provides for all routes of administration for drugs

Option Status: To be developed. Work underway, revisit topic in 1 year

10. Indication

Definition:" Indication describes the treatment, prevention or diagnosis of a recognized disease or condition or of an important manifestation of a disease or condition. It may also address the relief of symptoms associated with a disease or syndrome. It may recommend that it is administered with a primary mode of therapy and limit use to selected sub-groups. Indication may also identify specific tests needed for screening and monitoring and identify anticipated improvements as a result of use. The indication may refer to safety considerations and identify specific conditions that should be met before the drug is used on a long-term basis

Options to Consider:

1. Current practice: Indication as a text field
   No structured terminology is used to characterize indication in a more granular fashion
2. Indication represented as granular objects
   a. Analysis underway, revisit topic in 1 year.
   b. FDA contractor working to research an effective information object model and terminologies to characterize indication.

Option Status: Indication is a complex concept that requires the creation of an information model. Work underway by an FDA contractor to create the information model and to recommend supporting terminologies. , Care will need to be taken to ensure that elements from the indications information model that overlap with other areas, such as medical problems, are harmonized with other recommendations. We suggest revisiting the topic in 1 year.

11. Contraindications

Definition

Contraindications are those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration

of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state, "None known."

Type of sub-domain information needed:

Situations where drug should not be used

Hypersensitivity

Risk of harm due to age, sex, concomitant therapy, disease state, or other condition.

Adverse reactions and known hazards.

Options to Consider:

3. **Current practice: Indication as a text field**

   No structured terminology is used to characterize indication in a more granular fashion

4. **Indication represented as granular objects**
   a. Analysis underway, revisit topic in 1 year.
   b. FDA contractor working to research an effective information object model and terminologies to characterize indication.

Option Status: Contraindication is a complex concept that requires the creation of an information model. Work underway by an FDA contractor to create the information model and to recommend supporting terminologies. , Care will need to be taken to ensure that elements from the indications information model that overlap with other areas, such as medical problems, are harmonized with other recommendations. We suggest revisiting the topic in 1 year.

12. Drug Classifications

Definition

We group drugs into classes for at least 2 reasons. First, we group drugs so that we can aggregate data on specific drugs that share common characteristics. For example, it may be important to know how many people with upper respiratory infections are treated with fluoroquinolones (an aggregation of the specific drugs ciprofloxacin, levofloxacin, moxifloxacin, sparfloxacin, etc.). Second, we group drugs so that if information on a specific drug is not known, but information about a class of drugs is known, we can record that more general information. For example, we often collect information from paper records or from patients themselves, and information on the specific drug may not be available. (A patient might know that they have an allergy to cephalosporins but the

patient may not know name of the specific cephalosporin that caused an allergic reaction.)

Drugs may be grouped in many ways (e.g., mechanism of action, therapeutic intent, or pharmacokinetics). Therefore, one may choose a relatively simple classification system (in which one drug exists in only class) that appears to work for most situations. On the other hand, one may develop a more complicated classification scheme in which a single drug can have multiple relationships that allow one drug to be in multiple groupings.

Options to Consider

Simple classification schemes that are currently in use include:

1) National Drug Code Directory Classification system maintained by FDA http://www.fda.gov/cder/ndc
2) The ATC system apparently maintained by WHO http://www.whocc.no/atcddd/
3) AHFS, USP and others
4) Proprietary systems including Multum and First Databank

More complicated schemes or "reference terminologies" (RTs) for medications are less widely used and include:

1) NDF RT
2) Galen
3) Proprietary systems such as SNOMED®.

Option Status:

A number of classification schemes exist. We recognize that all drug classifications have been designed to meet certain specific needs, and therefore have likely have limitations in their ability to address other needs.

13 Medication Orders: Not in scope for Phase I CHI
14. Prescriptions: Not in scope for Phase I CHI
15. Supplies: Not in scope for Phase I CHI

16. Adverse Events

Definition. A number of definitions exist regarding instances of harm resulting from medication use.

1. Adverse Drug Event: Any injury related to the use of a drug.
2. Potential Adverse Drug Event: An incident when a drug-related injury was possible but did not actually occur.
3. Medication Error: An error in the process of ordering or delivering a medication, regardless of whether it resulted in an injury.
4. Adverse Drug Reaction: Any noxious, unintended and undesired effect of a drug at doses used in humans for prophylaxis, diagnosis, or therapy.

An adverse drug event requires an information model and a cast of supporting terminologies. The information model must describe properties of the medication and the noxious effects at a minimum. Other broad categories of information might include characteristics of the patient suffering from the adverse event, and details of the care setting in which the event took place.

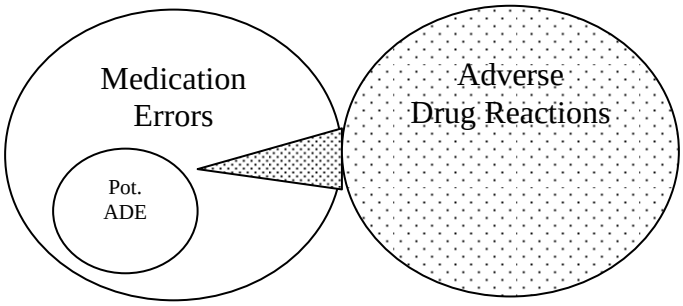

Figure 1. Classes of medication-related mishaps .

Figure 1, adapted from Bates, depicts the relationships between several classes of medication-related mishaps. Medication errors and adverse drug reactions combine to form the class of medication-related mishaps. Note that adverse drug reactions are not synonymous with adverse drug events. Adverse drug events, shown shaded in figure 1, include medication errors that result in patient injury (areas B+C) and adverse drug reactions. Medication errors that might cause patient injury are potential adverse drug events (fig. 1 area A). Innocuous medication errors are not classified as adverse drug events.

Options to Consider: MedDRA®, or some combination of information model directed terminologies such as RxNORM/NDF-RT, Micromedix, Multum, First Databank, Medispan, British Model, SNOMED CT® …

Option Status: Relatively immature, choice may not be possible at present.

17. Pharmacokinetics/Pharmacodynamics

Definition

Clinical Pharmacology. (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body

fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information. (2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances: (i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement ``The following in vitro data are available but their clinical significance is unknown." (ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in Sec. 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under Sec. 201.58 or Sec. 314.126(b) of this chapter.

Type of sub-domain information that may be desirable:

PK information for Biochemical and/or physiological entities
degree and rate of absorption,
pathways of biotransformation,
percentage of dose as unchanged drug and metabolites,
rate or half-time of elimination,
concentration in body fluids associated with therapeutic and/or toxic effects,
degree of binding to plasma proteins,
degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier

PK Information for clinical use[5]
Body compartment:Usually plasma but sometimes CSF or other compartment important for effectiveness of product
Subject/population approach
Cmax (mg/L)
Cmin
Tmax
T1/2
AUC (mg/L/hr)
Clearance (CL/kg)
Vd
Other(s)

PK Information for Drug Interactions

Risk level categories under evaluation by FDA

[5] ICH M4E, Presentations from Shiew Mei Huang

CYP enzyme X Substrate Y/N

Major pathway---->sensitive substrate one with a narrow therapeutic range
How sensitive is the NME to enzyme inhibition or induction by other (I&I) drugs?

X=CYP3A, CYP2D4, CYP2C, CYP1A2, CYP2E1
Inhibitor/Inducer(I&I)

Inhibitor

Potent/strong (>5 fold)
Moderate (2-5 fold)
Weak (<2 fold)

Options to Consider: the Human Cytochrome P450 (CYP) Allele Nomenclature (http://www.imm.ki.se/CYPalleles/), NDF-RT PK hierarchy, others

Option Status Immature**.** Pharmacokinetics and Pharmacodynamics are to be developed. Work underway, revisit topic in 1 year

18. Medication Labeling Headers

Definition

Drug labeling summarizes the essential scientific information needed for the safe and effective use of drugs and is controlled by the FDA, the regulatory body responsible for assuring the accuracy of labeling. Labeling content is based in regulation and for drug labeling includes the approved indications, effects, dosages, routes, methods, and frequency and duration of administration, relevant warnings, hazards, contraindications, side effects, and precautions and other information. In addition to providing comprehensive prescribing information, labeling must be current and updated whenever new information becomes available. As a result of the evidence-based approach and rigorous review, product labeling provides the most comprehensive, robust and well-maintained single source of clinical information on the safe and effective use of a drug product.

Options to Consider: HL7® CDA specification for medication label document structure.

Option Status – Moderately Mature, choice possible

Health Level Seven® is in the process of balloting a specification for drug product label information. This specification will standardize product labeling, and specify certain

terminology for product section headings and some product descriptors. The specification may achieve final approval during March/April 2004.

Selection Criteria

COMPLETELY BORROWED FROM HL7 VOCABULARY TECHNICAL COMMITTEE

1. **Content** *Domain coverage:* **Necessary**
2. **Concept Orientation**
    a. *Separation of meaning from name(s):* **Necessary**
    b. *Nonvagueness, nonredundancy, nonambiguity:* **Necessary**
3. **Concept Permanence**
    a. *Retirement, not deletion:* **Necessary**
    b. *Name changes don't change meaning:* **Necessary**
4. **Nonsemantic identifiers**
    a. *Not the name:* **Necessary**
    b. *Not a mnemonic:* **Desirable**
    c. *Not a hierarchical code* **Necessary**
    d. *Not a code that limits content:* **Desirable**
5. **Polyhierarchy**
    a. *Hierarchy:* **Desirable**
    b. *Polyhierarchy:* **Desirable**
    c. *Is-a relationships:* **Desirable**
6. **Formal definitions** **Desirable**
7. **Reject "Not Elsewhere Classified** **Desirable**
8. **Multiple Granularities** **Desirable**
9. **Multiple Consistent Views** **Desirable**
10. **Representing Context** **Irrelevant**
11. **Evolve Gracefully** **Necessary**
12. **Recognize Redundancy** **Desirable**
13. Mapping – **Necessary for certain subdomains**
14. Representation – must not have arbitrary restrictions, such as numbers of digits – **Necessary**
15. Maintenance **Necessary**
16. Context Free Identifiers – **Necessary**
17. Unique Identifiers – **Necessary**
18. Version Control – dated; obsolete marking – **Necessary**
19. Responsiveness – **Necessary**
20. Distribution – negligible cost; Internet – **Necessary**
21. Usage – public domain **Necessary**
22. Pricing – Distribution costs must not impose a barrier – **Necessary**

Subdomains –Detailed Analysis and Recommendations

Active Ingredient – see attached template

Clinical Drug – see attached template

Manufactured Dosage Form – see attached template

Finished Dosage Form – see attached template for products

The CHI medications group recommends use of FDA's National Drug Codes for finished dosage forms. We would also like the full Council to encourage the FDA to improve and revise NDC codes and NDC code generation processes in an expeditious fashion to address well-known issues.

Product – see attached template

The CHI medications group recommends use of FDA's National Drug Codes for products. We would also like the full Council to encourage the FDA to improve and revise NDC codes and NDC code generation processes in an expeditious fashion to address well-known issues.

Package – see separate report

Special Populations/Sub-populations

Analysis

Sub-groups of the population using medications for the treatment or prevention of medical conditions can demonstrate differences in the safety and effectiveness of these products. These differences may be attributable to intrinsic factors (e.g., genetic, clearance, disease condition), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Sub-populations that have demonstrated differences in response to drugs used to treat or prevent medical conditions include those grouped by age, race/ethnicity, sex and disease states or other physiologic impairment.

Differences in response to medical products have been observed in racially and ethnically distinct subgroups of the U.S. population. For example, in the United States, Whites are more likely than persons of Asian and African heritage to have abnormally low levels of an important enzyme (CYP2D6) that metabolizes drugs belonging to a variety of therapeutic areas, such as antidepressants, antipsychotics, and beta blockers (Xie 2001). Additionally, after using some drugs in the psychotherapeutic class, slower enzyme metabolism (CYP2C19) has been observed in persons in the United States of Asian descent as compared to Whites and Blacks (Xie 2001). Other studies have shown that Blacks respond poorly to several classes of antihypertensive agents (beta blockers and angiotensin converting enzyme (ACE) inhibitors) (Exner 2001 and Yancy 2001). Racial differences in skin structure and physiology have been noted that can affect response to dermatologic and topically applied products (Taylor 2002). Clinical trials have demonstrated lower responses to interferon-alpha used in the treatment of hepatitis C

among Blacks when compared to other racial subgroups (McHutchison 2000 and Reddy 1999).

Similarly, gender differences in response can include prolongation of the QT interval and result in the development of a life-threatening cardiac arrhythmia. Women may also respond differently depending upon their reproductive status. Pregnant and nursing women taking medications represent another level of concern for the safety and effectiveness of medications. Differences in response to therapeutic products are observed between the very young and the aged. Neonates and infants metabolize drugs differently compared to adults, as the physiologic mechanisms for metabolism and elimination of drugs have not fully matured. Geriatric patients are often prescribed several medications concurrently and may react when these drugs cannot be effectively eliminated. Finally, sub-groups of the population having certain disease conditions, for example, hepatic or renal disease, can impair an individuals ability to metabolize or eliminate a medical product making them more susceptible to an overdose of the product.

Recommendation

We recommend the use of HL7® vocabulary tables for the characterization of race and ethnicity and gender. These tables are non-proprietary sources of controlled vocabularies that are accessible in the HL7® RIM Vocabulary Tables. The Race and Ethnicity tables have been developed in collaboration between the CDC, the Census Bureau and HL7®. The benefit of these tables is that the OMB recommendations for characterizing Race and Ethnicity are provided in more detail and coded which allows more consistent representation of ancestral origins and enhances "mapping" between more granular representation of race and ethnicity and the OMB recommended five categories for race and two for ethnicity. This amount of detail is particularly important when considering international studies using this standard terminology to describe the ancestry of study participants, when studies are evaluated for relevance to U.S. populations.

Administration – deferred for 1 year followup

Indication - deferred for 1 year followup

Contraindications - deferred for 1 year followup

Drug Classifications

Recommendations

Currently, we are not aware of any single drug classification scheme that meets all the needs expressed by CHI medication sub group participants. We are aware of hierarchies that have been developed within the NDF-RT project for medication chemical structures, mechanism of action, physiologic effects, and therapeutic intents.

We suggest that the CHI council conditionally recommend the use of NDF-RT classification schemes for mechanism of action and physiologic effect when possible to avoid redundancy and promote interoperability in these areas. A disclaimer that recognizes that many classification needs will not be met by the partial recommendation should be issued concurrently. We also recommend that this CHI revisit this topic in the future.

Analysis

One of the desired qualities of a standardized medication terminology is the inclusion of hierarchical structures to categorize each medication. There are multiple clinically relevant methods for classifying medications, including mechanism of action, physiologic effects, intended therapeutic use, FDA approved indications, chemical structures, and other pharmacological properties. It is equally possible to imagine relevant non-clinical medication classification schemes as well. Furthermore, classification schemes may be applied to one or more different types of medication-related substances. (e.g., active ingredients and packaged products).

The most desirable classification scheme can only be determined by the intended use of the classification. For example, clinical decision support systems designed to promote patient safety via allergy checking may want to classify medications in a manner compatible with known allergic responses. Systems designed to reduce ordering of medications with the same mechanism of action (i.e., two beta blockers) need mechanism of action classification schemes. Classification schemes may benefit from hierarchical representation. For example, in certain circumstances it may be useful to know that Beta 1 receptor blockers and Beta 2 receptor blockers are both types of Beta-receptor blockers. Attempts to monitor the use of certain classes of medications among defined populations would be enhanced by a hierarchical structure.

Given the separate intended and multiple potential uses of medication data, it is desirable and perhaps necessary to encourage standard medication representations that accommodate multiple hierarchies. Any accepted vocabulary should be flexible enough to provide a hierarchical classification of medications and be able to evolve to include multiple hierarchies. (See other recommendations)

We are aware of hierarchies that have been developed within the NDF-RT project for medication chemical structures, mechanism of action, physiologic effects, and therapeutic intents. An “in press” publication[6] documents the content coverage and utility of the NDF-RT physiologic effect hierarchy. In our group’s experience, no other classification scheme systematically and fully dissects these important medication properties and studies of other classification schemes are lacking. Furthermore, RxNorm and NDF-RT drug components and clinical drugs are tightly integrated and RxNorm mappings to other

1. [6]Rosenbloom S.T et. al. Adequacy of representation of the National Drug File Reference Terminology Physiologic Effects reference hierarchy for commonly prescribed medications In press :Journal of the American Medical Informatics Association Fall Symposium Supplement 2003

drug terminologies are freely available. NDF-RT is in the late stages of development and will soon be freely available to the public. Thus, a wide audience could apply NDF-RT hierarchies in their systems with relatively low cost.

16. Adverse Events

Recommendations

Data pertaining to adverse drug events require an information model and a cast of supporting terminologies. We identify no single vocabulary that can acceptably fulfill all supporting terminology needs. Given that caveat, we recommend that:

1. The council adopts the medication working group's guidance on standards for referring to medication products to populate appropriate entities in the adverse drug event information model.
2. The council strive to ensure harmonization between the terminologies used to express medical problems caused by medications with terminologies used to express medical problems in general
3. The council carefully follows the ongoing work in creating an adverse drug event information model being conducted by the FDA.

Analysis

Adverse drug event vocabulary has several distinct applications. We identify no single vocabulary that can fulfill all these applications. The medication working group could attempt to limit the scope of adverse drug events to a single application; however, we do not recommend this approach because this could lead to multiple vocabularies for the same data depending on the purpose for which that data would be used. In addition, adverse drug events are a subset of adverse events resulting from the process of medical care and are often linked to medical errors. Thus, an adverse drug event requires an information model and a cast of supporting terminologies. The information model must describe properties of the medication and the noxious effects at a minimum. Other broad categories of information might include characteristics of the patient suffering from the adverse event, and details of the care setting in which the event took place. Therefore, adverse drug event vocabulary may need to be addressed in conjunction with other domains (e.g. – encounters or a new patient safety domain).

The applications of adverse drug event vocabulary include: (1) required regulatory oversight by FDA; (2) required or voluntary incident reporting by individual institutions, states, or federal authorities; (3) clinical care documentation and computerized decision support; and (4) facilitation of multi-center health services research. First, FDA requires adverse drug event reports from pharmaceutical companies as part of their regulatory role in monitoring drug safety. By international consensus, FDA requires that MedDRA®, a

proprietary vocabulary, be used for this reporting Second, incident reporting systems include, but generally are not limited to, adverse drug events. In addition, these systems vary considerably in the data elements they contain. Third, documenting, preventing, and treating adverse drug events is a core clinical function of healthcare. Lastly, a common adverse drug event vocabulary would facilitate multi-center initiatives designed to determine the scope and magnitude of adverse drug events and to evaluate interventions designed to reduce them. Any vocabulary for adverse drug events that is recommended should have a clearly documented, widely available mechanism to harmonize with other vocabularies.

Labeling Section Headers – see separate report

Appendix A

Information Exchange Requirements (IERs)

Information Exchange Requirement	Description of IER
Beneficiary Financial / Demographic Data	Beneficiary financial and demographic data used to support enrollment and eligibility into a Health Insurance Program.
Beneficiary Inquiry Information	Information relating to the inquiries made by beneficiaries as they relate to their interaction with the health organization .
Beneficiary Tracking Information	Information relating to the physical movement or potential movement of patients, beneficiaries, or active duty personnel due to changes in level of care or deployment, etc.
Body of Health Services Knowledge	Federal, state, professional association, or local policies and guidance regarding health services or any other health care information accessible to health care providers through research, journals, medical texts, on-line health care data bases, consultations, and provider expertise. This may include: (1) utilization management standards that monitor health care services and resources used in the delivery of health care to a customer; (2) case management guidelines; (3) clinical protocols based on forensic requirements; (4) clinical pathway guidelines; (5) uniform patient placement criteria, which are used to determine the level of risk for a customer and the level of mental disorders (6) standards set by health care oversight bodies such as the Joint Commission for Accreditation of Health Care Organizations (JCAHO) and Health Plan Employer Data and Information Set (HEDIS); (7) credentialing criteria; (8) privacy act standards; (9) Freedom of Information Act guidelines; and (10) the estimated time needed to perform health care procedures and services.
Care Management Information	Specific clinical information used to record and identify the stratification of Beneficiaries as they are assigned to varying levels of care.
Case Management Information	Specific clinical information used to record and manage the occurrences of high-risk level assignments of patients in the health delivery organization..
Clinical Guidelines	Treatment, screening, and clinical management guidelines used by clinicians in the decision-making processes for providing care and treatment of the beneficiary/patient.

Cost Accounting Information	All clinical and financial data collected for use in the calculation and assignment of costs in the health organization.
Customer Approved Care Plan	The plan of care (or set of intervention options) mutually selected by the provider and the customer (or responsible person).
Customer Demographic Data	Facts about the beneficiary population such as address, phone number, occupation, sex, age, race, mother's maiden name and SSN, father's name, and unit to which Service members are assigned
Customer Health Care Information	All information about customer health data, customer care information, and customer demographic data, and customer insurance information. Selected information is provided to both external and internal customers contingent upon confidentiality restrictions. Information provided includes immunization certifications and reports, birth information, and customer medical and dental readiness status
Customer Risk Factors	Factors in the environment or chemical, psychological, physiological, or genetic elements thought to predispose an individual to the development of a disease or injury. Includes occupational and lifestyle risk factors and risk of acquiring a disease due to travel to certain regions.
Encounter (Administrative) Data	Administrative and Financial data that is collected on patients as they move through the healthcare continuum. This information is largely used for administrative and financial activities such as reporting and billing.
Improvement Strategy	Approach for advancing or changing for the better the business rules or business functions of the health organization. Includes strategies for improving health organization employee performance (including training requirements), utilization management, workplace safety, and customer satisfaction.
Labor Productivity Information	Financial and clinical (acuity, etc.) data used to calculate and measure labor productivity of the workforce supporting the health organization.
Health organization Direction	Goals, objectives, strategies, policies, plans, programs, and projects that control and direct health organization business function, including (1) direction derived from DoD policy and guidance and laws and regulations; and (2) health promotion programs.
Patient Satisfaction Information	Survey data gathered from beneficiaries that receive services from providers that the health organization wishes to use to measure satisfaction.

Patient Schedule	Scheduled procedure type, location, and date of service information related to scheduled interactions with the patient.
Population Member Health Data	Facts about the current and historical health conditions of the members of an organization. (Individuals' health data are grouped by the employing organization, with the expectation that the organization's operations pose similar health risks to all the organization's members.)
Population Risk Reduction Plan	Sets of actions proposed to an organization commander for his/her selection to reduce the effect of health risks on the organization's mission effectiveness and member health status. The proposed actions include: (1) resources required to carry out the actions, (2) expected mission impact, and (3) member's health status with and without the actions.
Provider Demographics	Specific demographic information relating to both internal and external providers associated with the health organization including location, credentialing, services, ratings, etc.
Provider Metrics	Key indicators that are used to measure performance of providers (internal and external) associated with the health organization.
Referral Information	Specific clinical and financial information necessary to refer beneficiaries to the appropriate services and level of care.
Resource Availability	The accessibility of all people, equipment, supplies, facilities, and automated systems needed to execute business activities.
Tailored Education Information	Approved TRICARE program education information / materials customized for distribution to existing beneficiaries to provide information on their selected health plan. Can also include risk factors, diseases, individual health care instructions, and driving instructions.