ICO: Informed Consent Ontology, an introduction

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Ann Arbor, MI 48109 USA

In 2018 CTSOG ontology workshop, Little Rock, 2/27-28/2018:
http://ncorwiki.buffalo.edu/index.php/Ontology_of_Informed_Consent:_An_Approach_to_Specimen_and_Data_Sharing

Outline

- Introduce informed consent
- ICO development history and scope
- ICO development strategy and top level design
- ICO statistics, availability and web display
- VICO: ICO usage in vaccine domain
- Discussion

Informed Consent

Informed consent is a process for getting permission before conducting a healthcare intervention on a person, or for disclosing personal information. A health care provider may ask a patient to consent to receive therapy before providing it, or a clinical researcher may ask a research participant before enrolling that person into a clinical trial. Informed consent is collected according to guidelines from the fields of medical ethics and research ethics.

https://en.wikipedia.org/wiki/Informed_consent

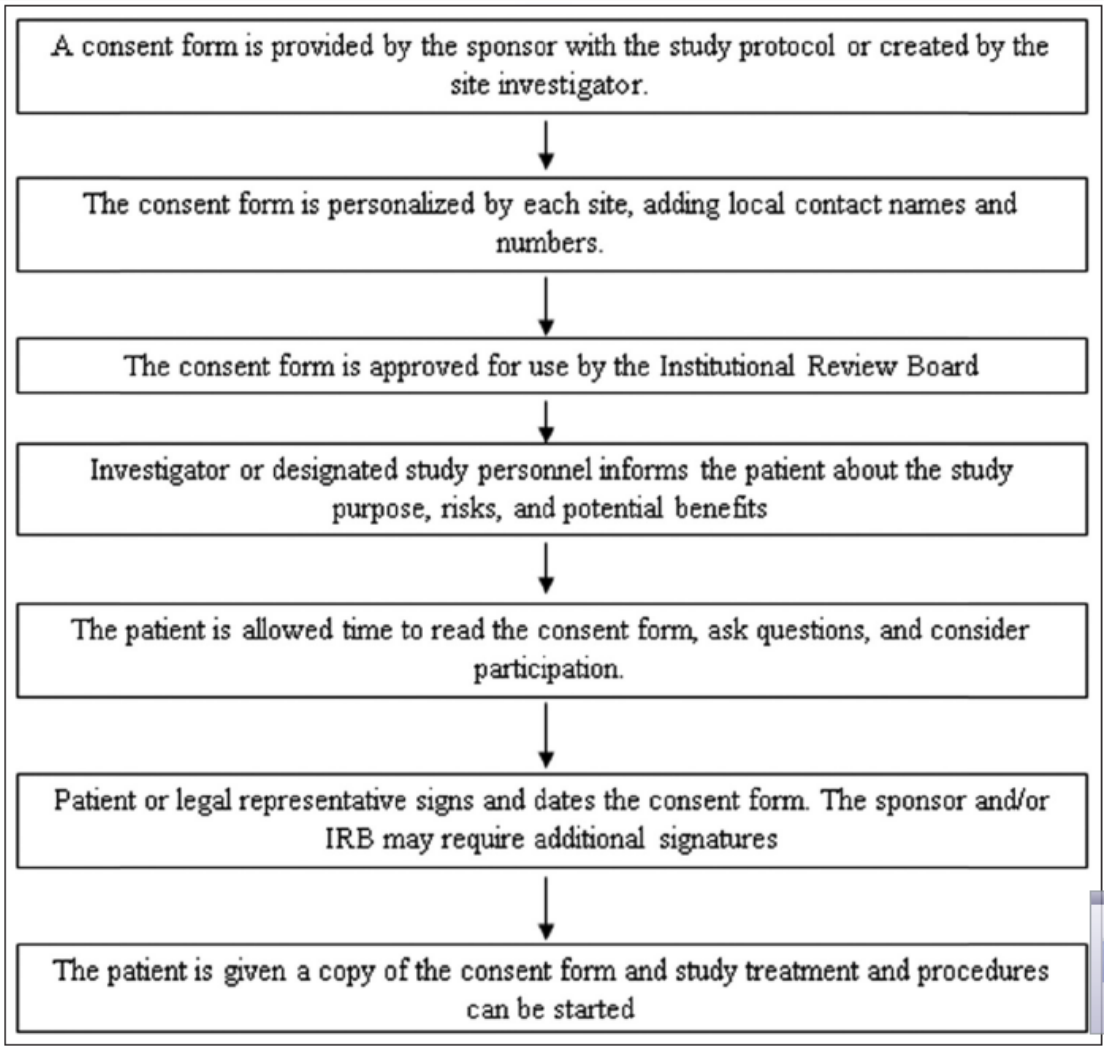
- Not only an ethical mandate but in many countries also a regulated requirement
  - USA Common Rule
- Electronic consent documents: know permitted uses and restrictions of data and materials.

Table 2: Classification of informed consent

	Classification[8,9]
Consent	An adult subject, capable of giving permission to participate in a research study, can provide consent. The subject must be 18 years of age and competent to make the decision to participate
Parental consent/ permission	When children/minors are included in research, the parent/guardian must sign a parental permission consent document. Some situations require permission from at least one parent, while other situations require permission from both parents. In some cases, it may be necessary to waive the requirement to obtain parental permission
Assent	Assent is a child's affirmative agreement to participate in research. If the subject is 7-17 years of age, assent must be obtained. The assent form must be written at the appropriate reading level of the youngest subject in the age range and use simple terminology
Verbal	Verbal consent still contains all elements of written consent; however, the participant is verbally read the elements and verbally agrees to participate
Short form	A "short form" is generally used when there is a language barrier and an IRB's approved consent is orally translated in the subject's native language

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3777303/

Various informed consent processes



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3777303/

Issues and challenges

- Informed consent standards not standardized
- Not computer understandable
- Data FAIRness issues – data should be:
  - Findable
  - Accessible
  - Interoperable
  - Re-usable.
- Needed: Community-based ontology

ICO: Informed Consent Ontology

- Community effort:
  - https://github.com/ICO-ontology/ICO
- Scope:
  - Modeling informed consent workflow and related entities
  - Modeling informed consent form generation, usage, and storage
- Driven by potential applications:
  - Automatic informed consent template generation
  - Informed consent validation
  - Biospecimen storage, processing, data release
  - …

Reference: Lin Y, Harris MR, Manion FJ, Eisenhauer E, Zhao B, Shi W, Karnovsky A, He Y: Development of a BFO-based Informed Consent Ontology (ICO). In: The 5th International Conference on Biomedical Ontologies (ICBO): 2014; Houston, Texas, USA, October 8-9, 2014. CEUR Workshop Proceedings; 2013: Page 84-86. [http://ceur-ws.org/Vol-1327/icbo2014_paper_54.pdf]

Original ICO development team

- Funding: a Univ. of Michigan MCubed project (2012-14)
- MCubed Co-PIs:
  - Alla Karnovsky
  - Marcelline R. Harris
  - Yongqun “Oliver” He
- Team members
  - Frank J. Manion
  - Asiyah Yu Lin (Ontologist, Oliver’s team)
  - Elizabeth Eisenhauer (Terminologist, Marcy’s team)
  - Bin Zhao (Programmer: IConect, Oliver’s team)
  - Wei Shi (Programmer: MediaWiki, Frank’s team)
- Consultants:
  - Dr. Nicholas H. Steneck
  - Dr. Blake J. Roessler

ICO development in UM

- Three templates:
  - From the Medical School Institutional Review Board (IRBMED) at University of Michigan (UM)
  - From the Health Sciences and Behavioral Sciences Institutional Review Board (IRB-HSBS) at UM
  - A consent form used for biobank.
- Three terminology repositories:
  - National Library of Medicine's Unified Medical Language System (UMLS®) Metathesaurus
  - National Center for Biomed Ontology (NCBO) BioPortal
  - Ontobee: OBO foundry ontologies linked server.

ICO development in UM (Cont'd)

- Find mapped terms and definitions:
  - National Cancer Institute Thesaurus (NCIt)
  - the Biomedical Research Integrated Domain Group (BRIDG)
  - the Ontology of Clinical Research (OCRe)
  - the Consumer Health Vocabulary (CHV)
  - the University of California San Diego permission ontology
- Outcome: Proceeding paper in ICBO 2014

Reference: Y. Lin, M. R. Harris, F. J. Manion, E. Eisenhauer, B. Zhao, W. Shi, et al., "Development of a BFO-based Informed Consent Ontology (ICO)," in **The 5th International Conference on Biomedical Ontologies (ICBO), Houston, Texas, USA, October 8-9, 2014**, 2014, pp. Page 84-86. [http://ceur-ws.org/Vol-1327/icbo2014_paper_54.pdf]

New ICO Developers – Biobanking focus

- **MUSC**
  - Jihad Obeid
- **UPenn:**
  - Chris Stoeckert, Jie Zheng, Mark Miller
- **UAMS**
  - Mathias Brochhausen - d-acts
- **Duke**
  - Helena Ellis, Anna Maria Masci
- Biobanking Ontology and biobanking cases
- Joint grant applications

Biobank Specimen Use Cases

From: Stoeckert, Christian <stoeckrt@pennmedicine.upenn.edu> Sent: Fri 2/23/2018 11:18
To: Obeid, Jihad; Manion, Frank; He, Oliver; MBrochhausen@uams.edu
Cc:
Subject: competency questions for the workshop

Use cases provided by participating biobanks:

We will test the ability of OBIB (enriched with representation from ICO) to aid searches through use cases defined as common requests that would benefit from semantic harmonization. Initial driving use cases to be applied at the source biobank are:

Penn Use Case: "Identify cases and controls from a population of patients that have EDTA blood or DNA specimen available who have consented to be recontacted. Match these based on blood pressure prescription and diagnosis data from the patient's EHR. Also match basic demographic data (age, weight, gender, race) collected at the time of recruitment." The case and control components of the search have already been successfully performed (as described earlier in Aim 1) and consent will be addressed next. This use case can also be used for cross-institutional testing at Duke.

Duke Use Case: "Identify large or small, normal tissue, intestine samples –from the Pathology paraffin archives, from patients with Parkinson's disease who have consented to a Broad Consent protocol (e.g., one from Duke that allows access to retrospective as well as prospective excess tissue)." This use case can also be used for cross-institutional testing at Penn.)

MUSC Use case: "Identify patients who were admitted to the Medical Intensive Care Unit, age >= 18, who ***do not*** have any of the ICD-9 codes that correspond to: Pneumonia, UTI, Bacteremia, Meningoencephalitis, …, and who ***do*** have a plasma sample in the Biorepository that has been consented for allowable use of specimens."

Michigan Use case 4: "Identify specimens available for research use for researchers engaged in a patient centered outcomes research network (PCORnet) across a US network of greater than 75 million patient records." The use case comes from Michigan's participation in PCORnet CDRN.

Informed Consent work in UTHealth/UM

- Led by **Cui Tao** at UTHealth, Houston
- UM:
  - Marcelline R. Harris
  - Frank Manion
  - Yongqun “Oliver” He
- Common Rule Ontology (CRO)
- U01 funding:
  - Project Title: Metadata applications on informed content to facilitate biorepository data regulation

ICO in China

- Informed consent is also a big issue in China

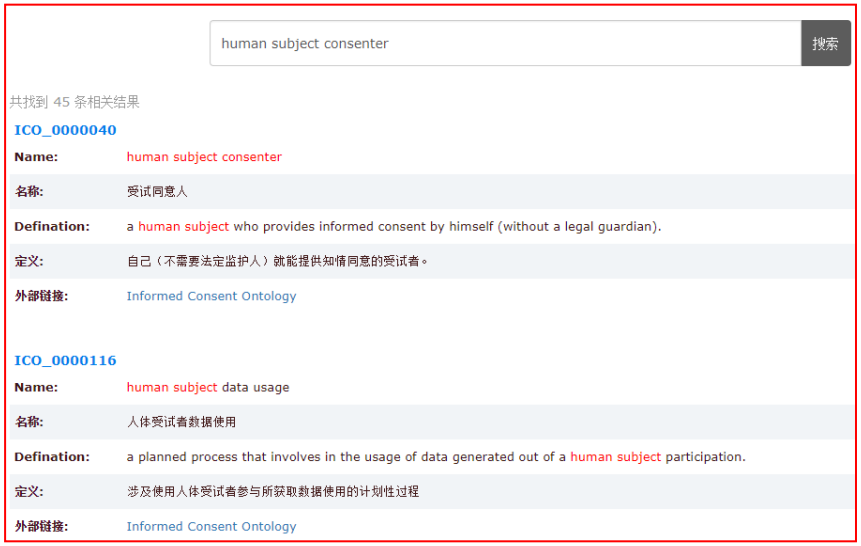
- ICO is translated to Chinese
- http://59.110.45.173/icochina/about
- Part of: Translational Oncology/Translational Cancer Research project

- Led by Prof. **Jian Guan** from Chinese Academy of Medical Sciences, Beijing
- **Funding**: National Scientific Data Sharing Platform for Population and Health

Jian Guan M.D. Lawyer
Contact information: E-mail and Phone Number:
E-mail: gjpumch@126.com; Phone: 086-010-69155816
Organization(s): Peking Union Medical College Hospital, PUMC & CAMS, Beijing, China
Position:
Professor, Health management; Peking Union Medical College
Associate Professor, Pathology, Department of Pathology, Peking Union Medical College Hospital
Executive Vice Director, Clinical Center (PUMCH); Director, Special Service Platform for Translational Medicine of Oncology, National Population and Health Scientific Data Sharing Platform;, Peking Union Medical College Hospital
Deputy Secretary-General, Chinese Society of Medical Science Research

ICO in China

- Website:
  - http://59.110.45.173/icochina
  - Translate ICO to Chinese



More Use Cases

- To be discussed today:

11:15am: Use cases - Facilitator: Mathias Brochhausen

1. Sharing specimens across protocols (MB)
2. Generation of electronic informed consent forms (JO)
3. Rights and obligations derived from informed consent analysis (FM)
4. Kidney Precision Medicine Project (OH)

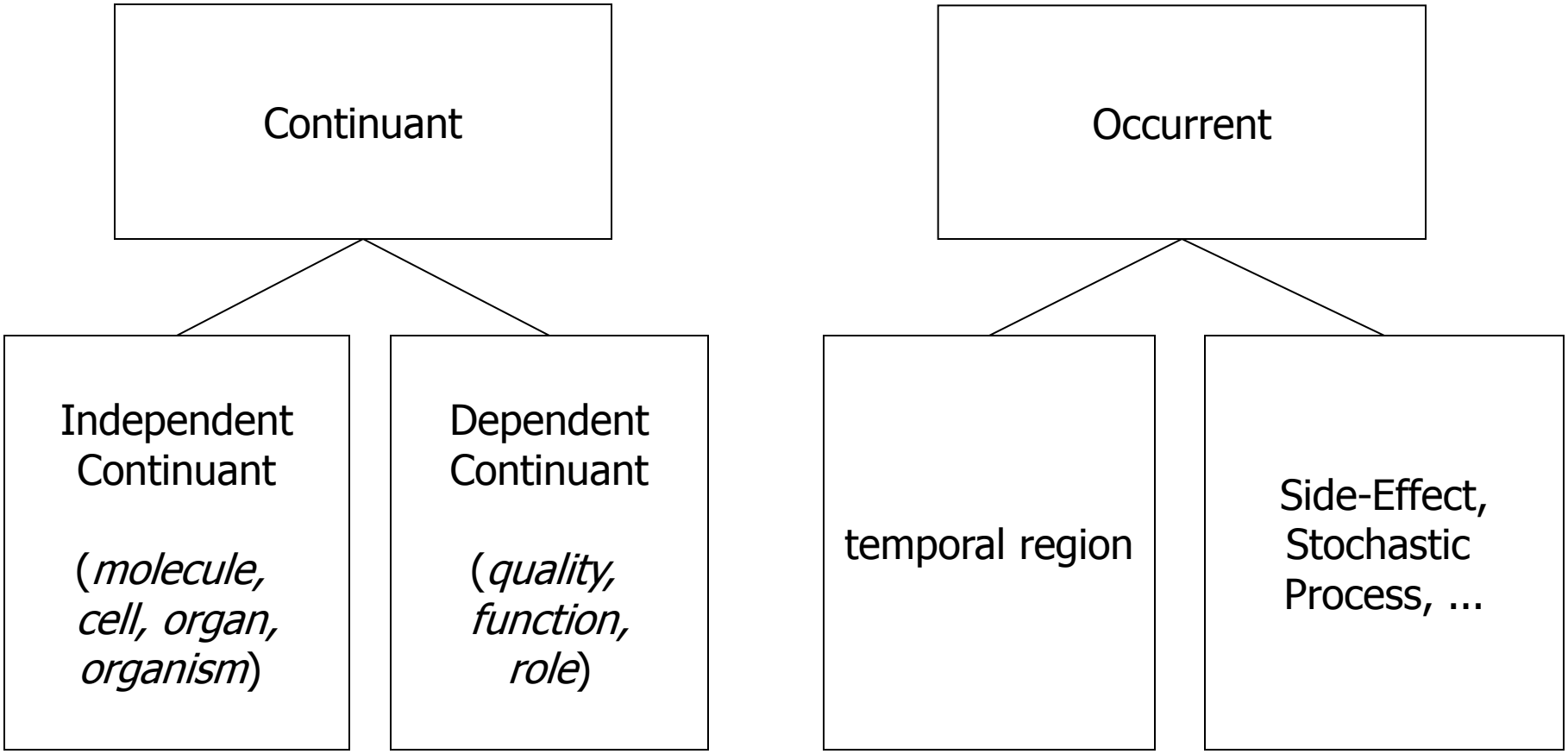
http://ncorwiki.buffalo.edu/index.php/Ontology_of_Informed_Consent:_An_Approach_to_Specimen_and_Data_Sharing

- KPMP (Kidney Precision Medicine Project) is a NIH-NIDDK newly funded initiative program – ontology plays a big role.

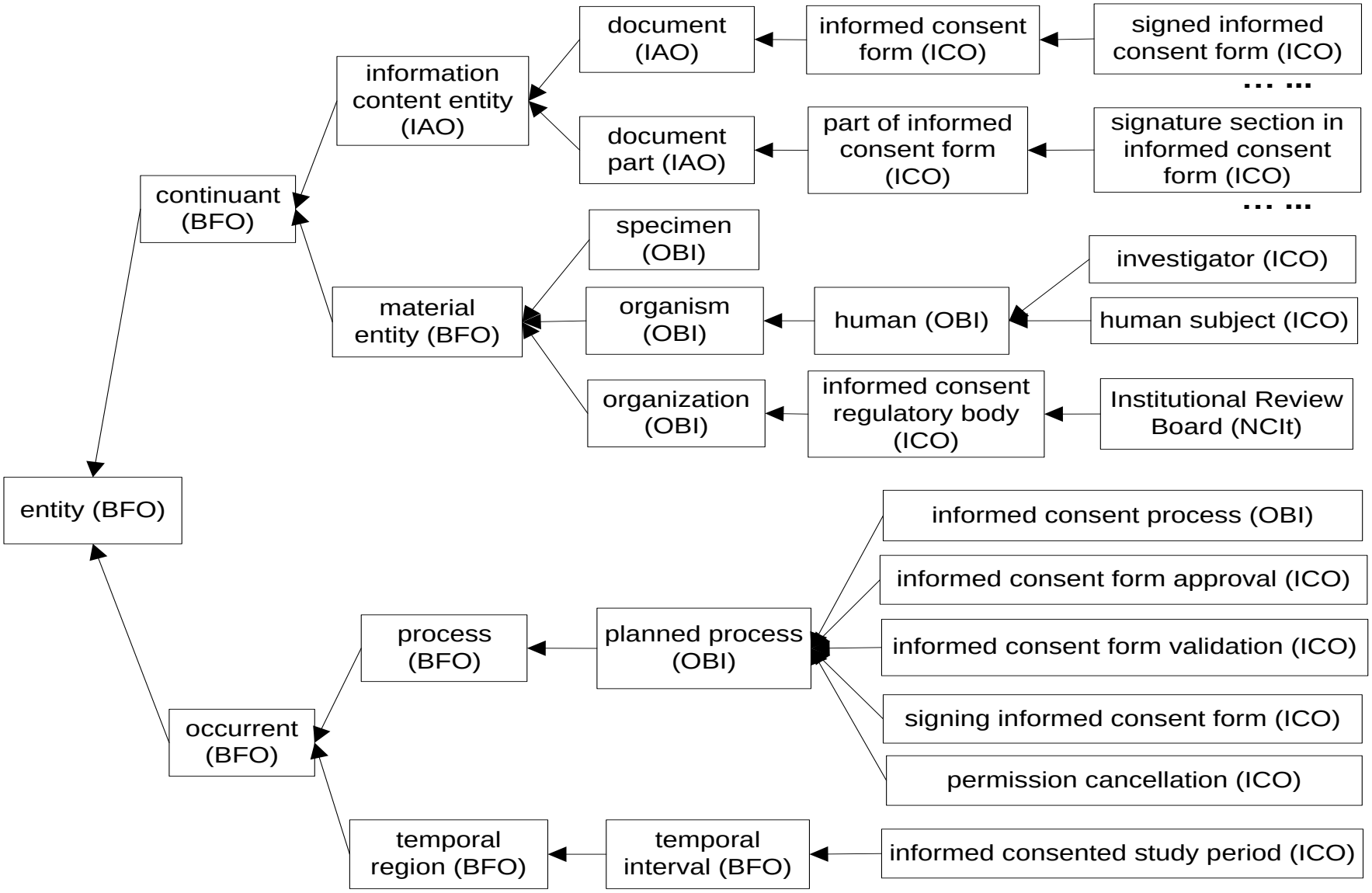
ICO Development Strategy

- Top-down and bottom-up
- **Top-down**:
  - Use BFO as top ontology, importing OBI (Ontology for Biomedical Investigation) and IAO(Information Artifact Ontology) → initial development
- **Bottom-up**:
  - Define concepts from Informed Consent templates and preferred terms from published terminologies -> expand the initial ontology
- Review and refine the definitions and relations between terms.

BFO (Basic Formal Ontology)



ICO Hierarchy



ICO Availability

- GitHub:
  - https://github.com/ICO-ontology/ICO
- Issue Tracker:
  - https://github.com/ICO-ontology/ICO/issues
- Web browsing:
  - Ontobee: http://www.ontobee.org/ontology/ico
  - BioPortal: https://bioportal.bioontology.org/ontologies/ICO

ICO Statistics

- Class (409)
- ObjectProperty (46)
- DatatypeProperty (3)
- AnnotationProperty (51)
- Instance (15)

Index	Ontology Prefix	Class	ObjectProperty	DatatypeProperty	AnnotationProperty	Instance	Total
1	BFO	35	6	0	2	0	43
2	CARO	2	0	0	0	0	2
3	CHEBI	5	0	0	0	0	5
4	CL	3	0	0	0	0	3
5	IAO	40	6	1	15	9	71
6	ICO	150	3	0	3	0	156
7	NCBITaxon	13	0	0	0	0	13
8	OAE	1	0	0	0	0	1
9	OBI	124	9	1	2	0	136
10	OGMS	5	0	0	0	0	5
11	OMRSE	3	1	0	0	0	4
12	PATO	4	0	0	0	0	4
13	REO	2	0	0	0	0	2
14	RO	0	21	0	1	1	23
15	Thesaurus.owl	14	0	0	0	0	14
16	UBERON	4	0	0	0	0	4
17	UO	1	0	0	0	0	1
18	doap	1	0	1	1	0	3
19	oboInOwl	1	0	0	6	0	7
20	owl	1	0	0	1	0	2
21	protege	0	0	0	1	0	1
22	rdf-schema	0	0	0	4	0	4
23	subsets	0	0	0	1	0	1
24	NoPrefix	0	0	0	14	5	19
Total	-	409	46	3	51	15	524

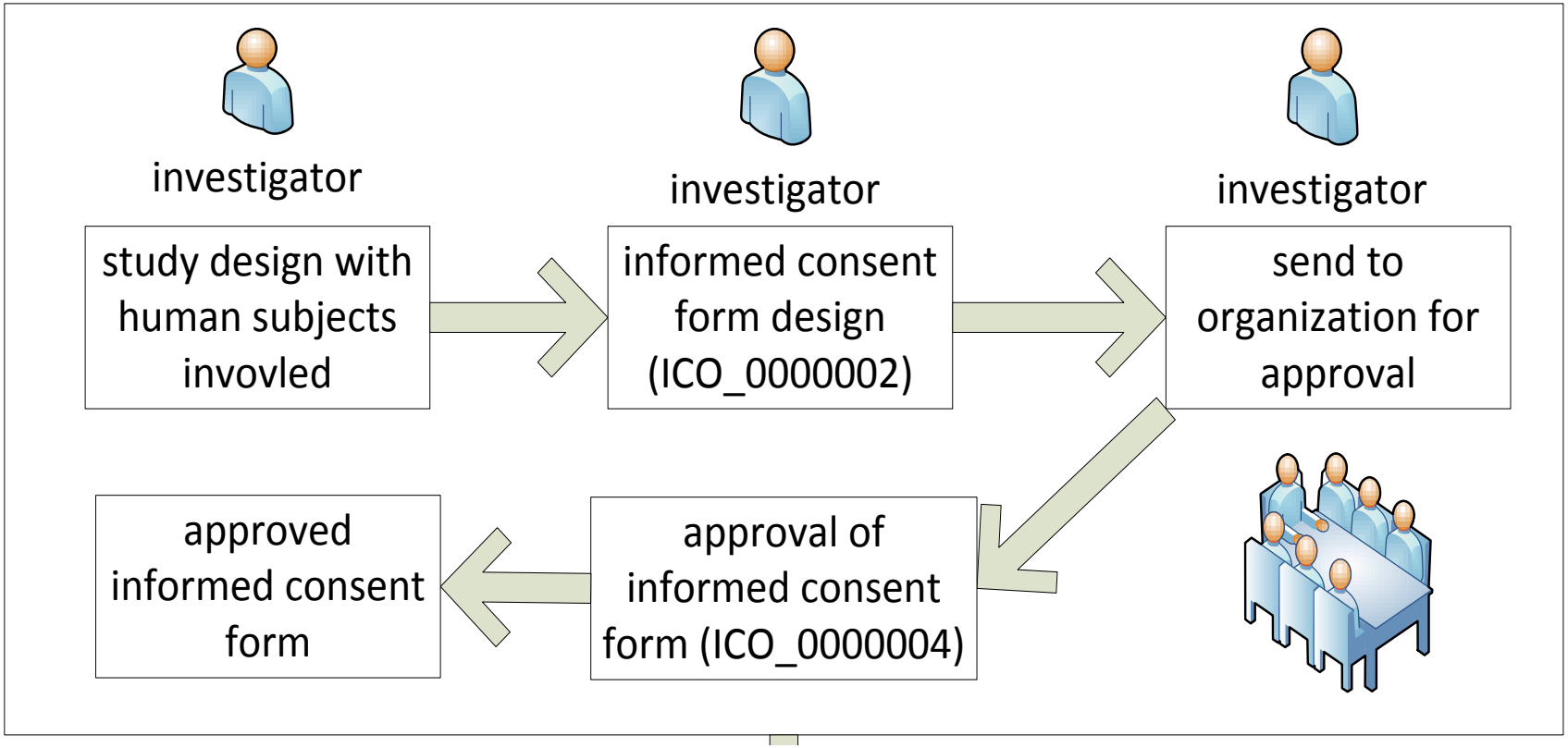
Cited from:

http://www.ontobee.org/ontology/ico

Informed consent work flow: in a typical clinical study

- Pre-Informed Consent Processes
  - *Informed consent form designing*
  - *Informed consent form approval*
- Processes of obtaining informed consent
  - *Study subject recruiting*
  - *Explaining the informed consent form*
  - *Study subject signing the informed consent form*
- Post informed consent documentation processes
  - *Study executing*
  - *Subject withdrawl*
  - *Data sharing and administration*
  - *Informed consent information administration*

Pre-informed consent processes



Obtaining informed consent

Investigator
Or
Research assistant

Inform candidate about study purpose, risks, benefits and other information in an informed consent document

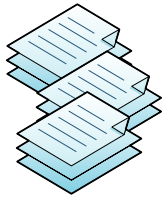
human subject candidate
OR

Legal guardian of the candidate

Different dimensions of consenting

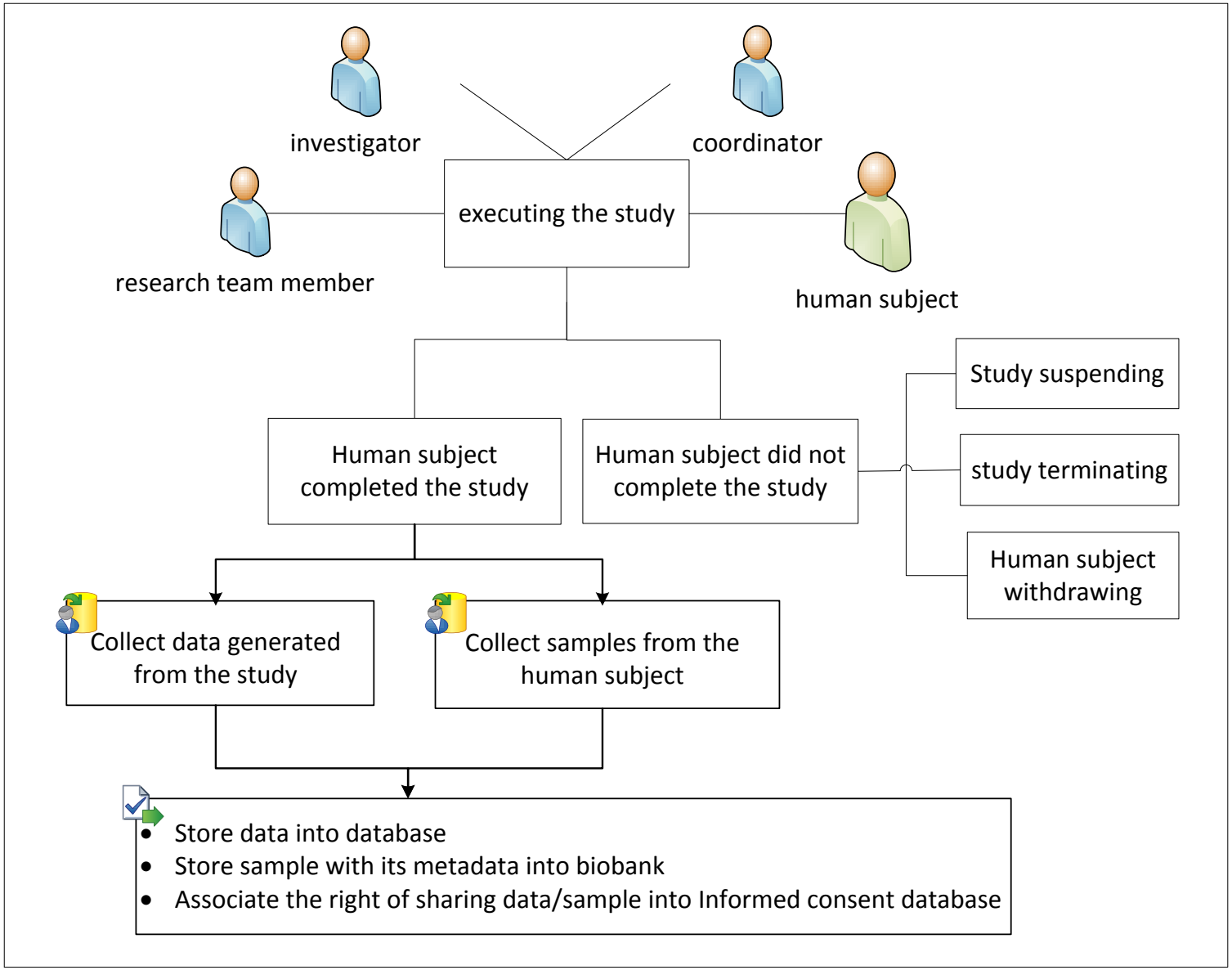
1. agree with participating protocol
2. agree with benefits and risks
3. agreement on samples process and uses
4. agreement on data derived from study
5. agreement about record confidentiality

Signing informed consent form

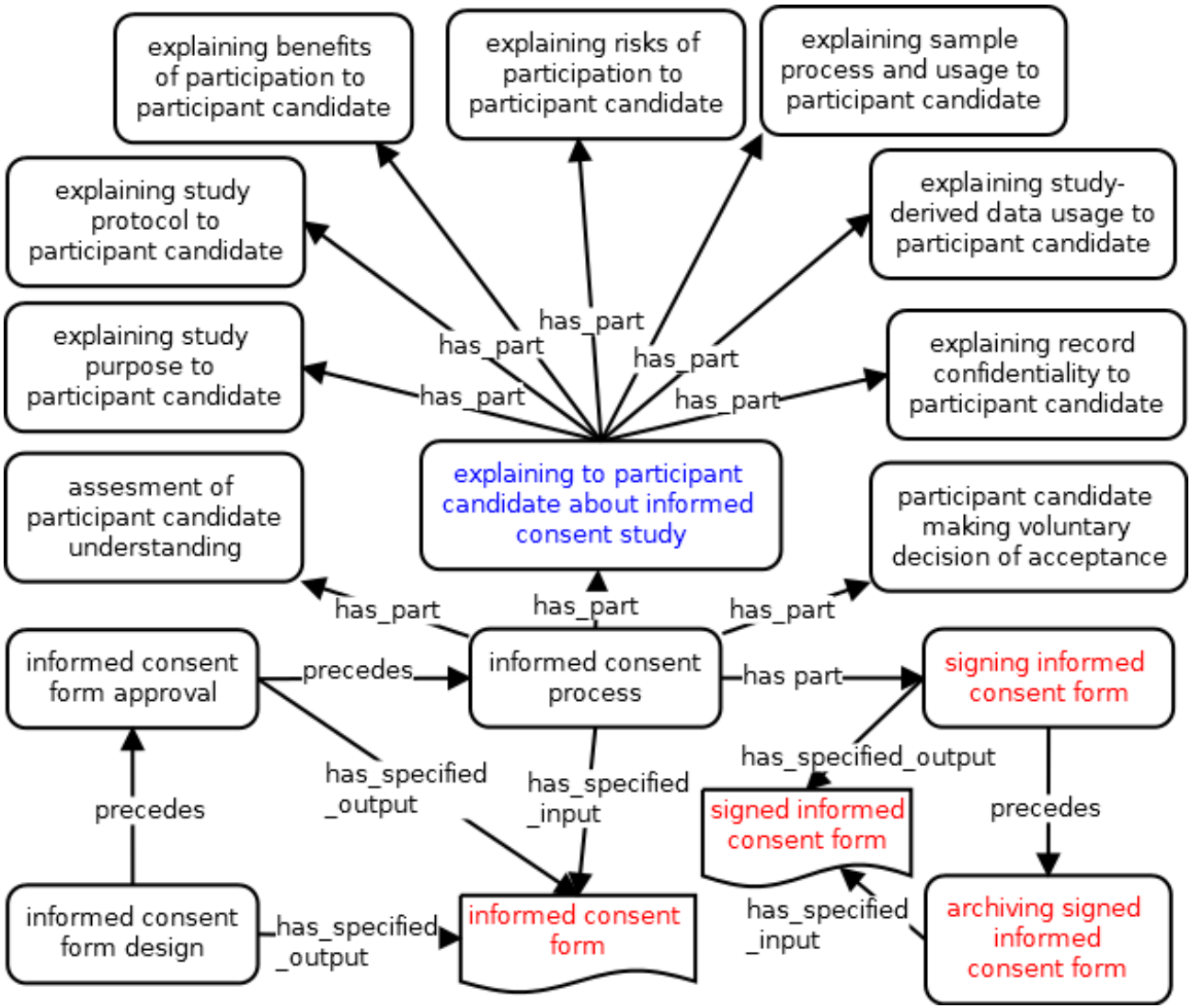


Signed consent form

Post informed consent process



Focus: Informed Consent form



Use case: Vaccination informed consent forms

COSTCO PHARMACY

Immunization Consent Form

PRECAUTIONS AND CONTRAINDICATIONS (Please check yes or no for each question.)

1. Are you sick today? ○ Yes ○ No
2. Do you have allergies to medications, food or vaccines? ○ Yes ○ No
   Allergies
3. Have you ever had a serious reaction after receiving a vaccination? ○ Yes ○ No
4. Do you have a long-term health problem with heart disease, lung disease, asthma, kidney disease, metabolic disease (e.g., diabetes), anemia or other blood disorder? ○ Yes ○ No
5. Do you have cancer, leukemia, AIDS or any other immune system problem? ○ Yes ○ No
6. Do you take cortisone, prednisone, other steroids or anti-cancer drugs, or have you had X-ray treatments? ○ Yes ○ No
7. Have you had a seizure, brain or nerve problem? ○ Yes ○ No
8. During the past year, have you received a transfusion of blood or blood products, or been given a medicine called immune (gamma) globulin? ○ Yes ○ No
9. For women: Are you pregnant or is there a chance you could become pregnant during the next month? ○ Yes ○ No
10. Have you received any vaccinations in the past 4 weeks? ○ Yes ○ No
    If yes, what vaccines?
11. Are you allergic to eggs? ○ Yes ○ No
12. Are you allergic to latex? ○ Yes ○ No

Walgreens healthcare clinic at select Walgreens

All vaccines

1. Are you currently sick with a moderate to high fever, vomiting/diarrhea? ☐ Yes ☐ No ☐ Don't know
2. Have you ever fainted or felt dizzy after receiving an immunization? ☐ Yes ☐ No ☐ Don't know
3. Have you ever had a reaction after receiving an immunization? ☐ Yes ☐ No ☐ Don't know
4. Do you have an immunocompromising condition (e.g., cancer, leukemia, lymphoma, HIV/AIDS, transplant), functional, or anatomic asplenia, CSF leak or cochlear implant? ☐ Yes ☐ No ☐ Don't know
5. Do you have allergies to latex, medications, food or vaccines? (Examples: eggs, bovin neomycin, phenol, yeast or thimerosal)
   a. If yes, please list:
6. Have you ever had a seizure disorder for which you are on seizure medications, a brai other nervous system problems?
7. **For women:** Are you pregnant or considering becoming pregnant in the next month?

Live vaccines (Chicken pox, flu nasal spray, MMR, oral typhoid, shingles, Yellow
Only answer these questions if you are receiving any immunization listed above.

8. Are you currently on home infusions, weekly injections (such as adalimumab, infliximab methotrexate, azathioprine or 6-mercaptopurine, antivirals, anticancer drugs or radiati
9. Have you received any vaccinations or skin tests in the past four weeks?
   a. If yes, please list:
10. Have you received a transfusion of blood, blood products or been given a medication in the past year?
11. Are you currently taking high-dose steroid therapy (prednisone >20mg/day or equivale
12. Do you have a history of thymus disease (including myasthenia gravis), thymoma or pr
13. Are you currently taking any antibiotics or antimalarial medications? (Oral typhoid only)
14. Do you have a history of thrombocytopenia or thrombocytopenic purpura? (MMR only)

Flu nasal spray (FluMist® Quadrivalent)

15. For patients 18 years of age and younger only: Are you receiving aspirin therapy or aspirin-containing therapy? ☐ Yes ☐ No ☐ Don't know
16. For patients 5 years of age and younger only: Is there a history of asthma or wheezing? ☐ Yes ☐ No ☐ Don't know
17. Do you have a nasal condition serious enough to make breathing difficult, such as a very stuffy nose? ☐ Yes ☐ No ☐ Don't know

Manitoba

B. Health History of Client

1. Are you well today? ☐ Yes ☐ No
   If no, describe
2. Do you have any allergies? ☐ Yes ☐ No
   If yes, describe
3. Have you ever had a serious reaction or condition following any vaccine? ☐ Yes ☐ No
   If yes, describe
4. Do you have any conditions that require regular visits to a doctor? ☐ Yes ☐ No
   If yes, please discuss with immunizer
5. Are you taking any medication that affects blood clotting? ☐ Yes ☐ No
   If yes, please list

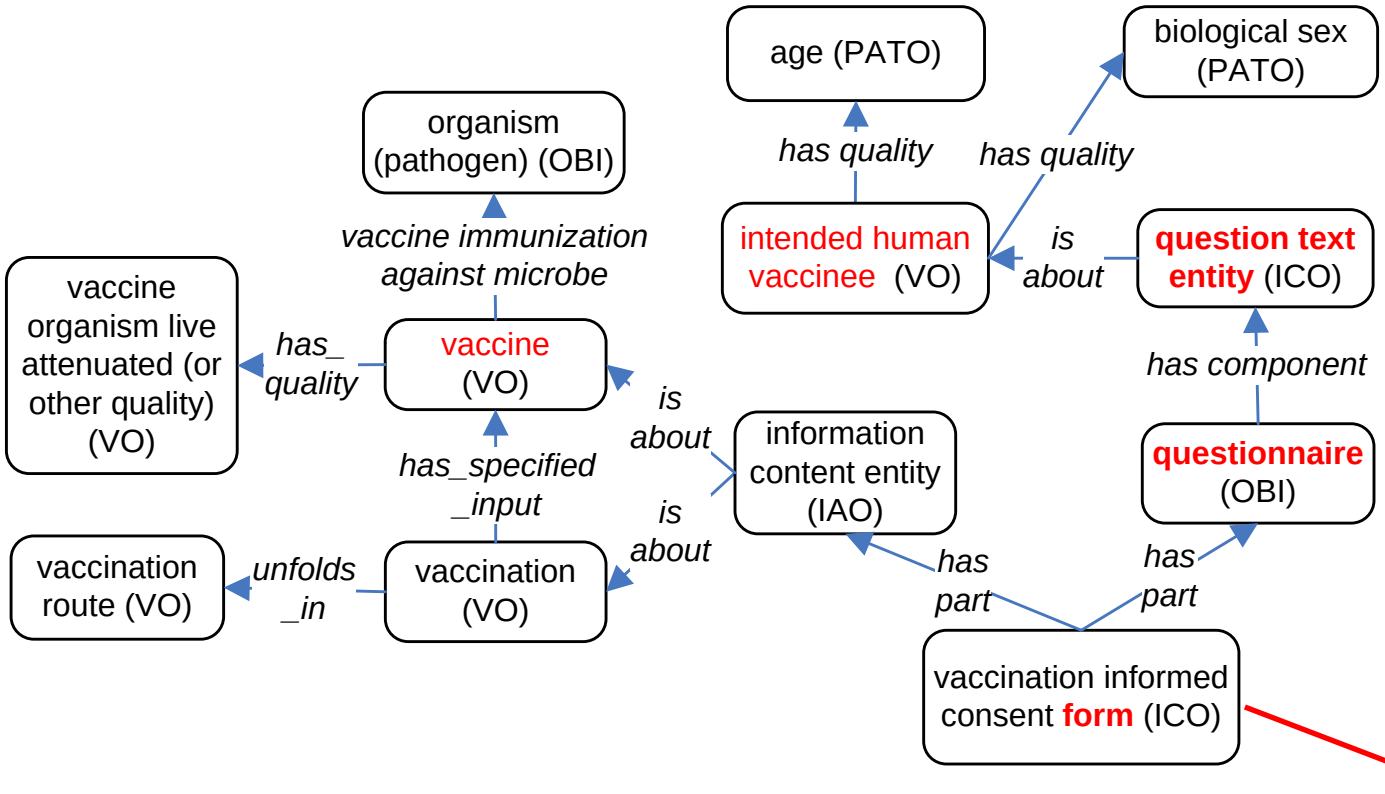
Vaccination Informed Consent Ontology (VICO) Develop and Applications

- VICO development:
  - Extend **ICO** and **Vaccine Ontology (VO)**
  - Goal: To organize vaccination informed consent-related entities and their relations
  - Focus: represent different vaccination informed consent forms → Support consistent representation of immunization questionnaires

- VICO applications:
  - Hypothesis: Enable systematic form comparisons & patients' informed consent data query and analysis
  - Use cases:
    - Class level knowledge query
    - Instance level detection of patients not recommended for certain vaccine immunization

Reference: Lin Y, Zheng J, He Y. VICO: Ontology-based representation and integrative analysis of vaccination informed consent forms. *J Biomed Semantics*. 2016 Apr 19;7:20. PMID: 27099700. PMCID: PMC4837519.

Basic VICO Design Pattern



From various sources:

- Costco
- Walgreens
- Manitoba

Focus: questions in questionnaires in forms vaccines for pathogens from companies

Use case 1. Comparison of different informed consent forms

SPARQL query:

```
PREFIX rdf: <http://www.w3.org/1999/02/22-rdf-syntax-ns#>
PREFIX owl: <http://www.w3.org/2002/07/owl#>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX xsd: <http://www.w3.org/2001/XMLSchema#>
PREFIX obo: <http://purl.obolibrary.org/obo/>
PREFIX questionnaire: <http://purl.obolibrary.org/obo/OBI_0001000>
PREFIX has_component: <http://purl.obolibrary.org/obo/RO_0002180>
SELECT ?question
WHERE
{
 ?questionnaire1 rdfs:subClassOf questionnaire: .
 ?questionnaire1 rdfs:subClassOf ?questionnaire1_axiom .
 ?questionnaire1 rdfs:label ?label1 .
 ?questionnaire1_axiom owl:onProperty has_component:; owl:someValuesFrom ?question .
 ?questionnaire2 rdfs:subClassOf questionnaire: .
 ?questionnaire2 rdfs:subClassOf ?questionnaire2_axiom .
 ?questionnaire2 rdfs:label ?label2 .
 ?questionnaire2_axiom  owl:onProperty has_component:; owl:someValuesFrom ?question .
 FILTER REGEX(str(?label1), "Costco") .
 FILTER REGEX(str(?label2), "Walgreens") .
}
```

question
'question whether allergic to vaccine'
'question on cancer'
'question whether currently sick'
'question on leukemia'
'X-ray treatment question'
'question on vaccination in past 4 weeks'
'question on asthma or wheezing history'
'seizure disorder question'
'question on blood transfusion in past year'
'question whether allergic to latex'
'question on woman pregnancy'
'question whether allergic to egg'
'question whether allergic to medication'

SPARQL query: Shared questions in **Costco** and **Walgreens** consent forms. (Done with Protégé)

	Question	Walgreens / Costco
1	question on vaccination in past 4 weeks	Walgreens; Costco
2	question on blood transfusion in past year	Walgreens; Costco
3	question whether allergic to vaccine	Walgreens; Costco
4	question on asthma or wheezing history	Walgreens; Costco
5	question on leukemia	Walgreens; Costco
6	question whether allergic to medication	Walgreens; Costco
7	seizure disorder question	Walgreens; Costco
8	question on cancer	Walgreens; Costco
9	question whether allergic to egg	Walgreens; Costco
10	X-ray treatment question	Walgreens; Costco
11	question whether allergic to latex	Walgreens; Costco
12	question on woman pregnancy	Walgreens; Costco
13	question whether currently sick	Costco
14	question on long-term heart disease	Costco
15	cortisone treatment question	Costco
16	immunocompromisation question	Costco
17	question on reaction after immunization	Costco
18	question on whether fainted or felt dizzy after immunization	Walgreens
19	question on skin test in past 4 weeks	Walgreens
20	question whether currently sick with a moderate to high fever, vomiting/diarrhea	Walgreens
21	question on serious nasal condition	Walgreens
22	question on high-dose steroid therapy for longer than 2 weeks	Walgreens
23	question on thymus disease	Walgreens
24	question on current aspirin therapy	Walgreens
25	question on current antibiotics usage	Walgreens

Comparison of questions listed in **Walgreens** and **Costco** vaccination informed consents

Use case 2. Identification of vaccination contraindications & patients who cannot be vaccinated (*e.g.*, egg allergen)

Egg allergy patients cannot be vaccinated by a vaccine containing a trace of egg product

SPARQL Query Question:

What vaccines have egg protein allergen?

```
PREFIX owl: <http://www.w3.org/2002/07/owl#>
PREFIX has_vaccine_allergen: <http://purl.obolibrary.org/obo/VO_0000531>
PREFIX chicken_egg_protein_allergen: <http://purl.obolibrary.org/obo/VO_0000912>

SELECT distinct ?vaccine ?VO_ID
FROM <http://purl.obolibrary.org/obo/merged/VICO>
WHERE {
        ?VO_ID rdfs:label ?vaccine .
        ?VO_ID rdfs:subClassOf ?VO_parent .
        ?VO_parent owl:onProperty has_vaccine_allergen:;
            owl:someValuesFrom chicken_egg_protein_allergen: .
}
```

Output format: Table Max Rows: 20

Run Query | Reset

Result | Raw Request/Permalinks | Raw Response

vaccine	VO_ID
Afluria	http://purl.obolibrary.org/obo/VO_0000006
FluLaval	http://purl.obolibrary.org/obo/VO_0000043
FluMist	http://purl.obolibrary.org/obo/VO_0000044
Fluvirin	http://purl.obolibrary.org/obo/VO_0000046
Fluzone	http://purl.obolibrary.org/obo/VO_0000047
YF-Vax	http://purl.obolibrary.org/obo/VO_0000121
Agriflu	http://purl.obolibrary.org/obo/VO_0001126
FSME - IMMUN	http://purl.obolibrary.org/obo/VO_0010714

Two steps:

1) **Find if a vaccine contains egg allergen.**
2) Find patients who are allergic to egg.

Shown was done using Protégé SPARQL

Note: Ontobee SPARQL can also be used with minor code change.

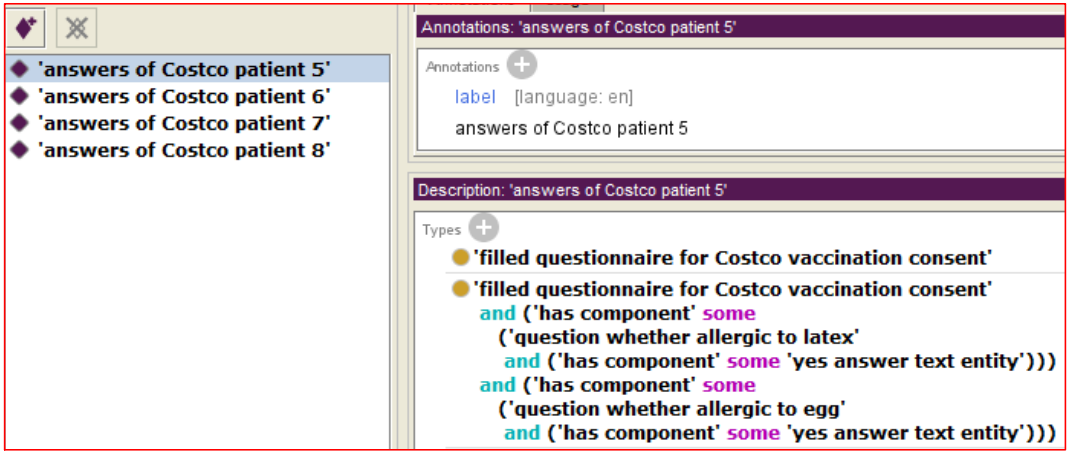
Use case 2. Identification of vaccination contraindications & patients who cannot be vaccinated (*e.g.*, egg allergen)

Two steps:

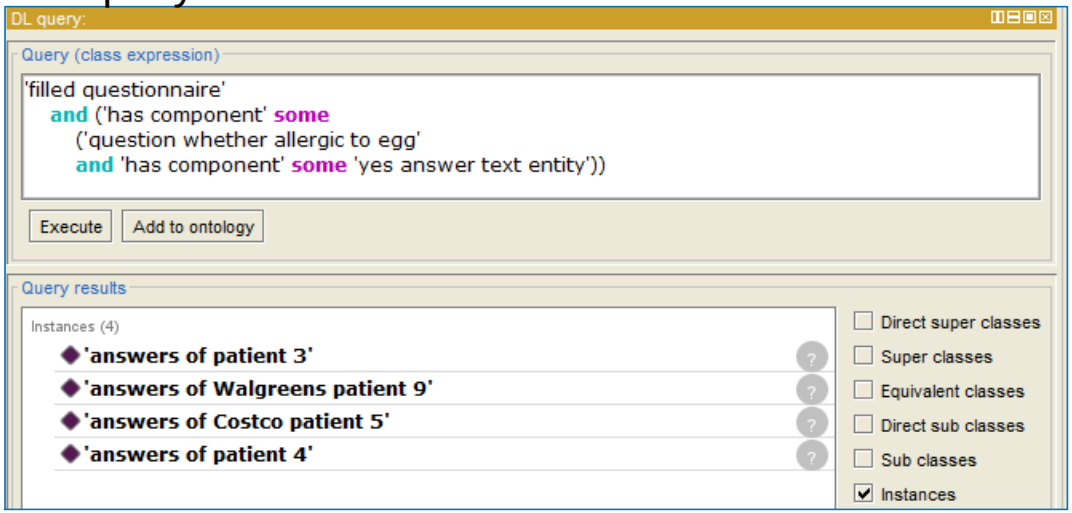
1) Find if a vaccine contains egg allergen.

2) **Find patients who are allergic to egg.**

Answers of a Costco patient



DL query and its results



(Done in Protégé OWL editor)

Discussion

- How to further develop ICO?
  - *More use cases*
  - …
- ICO applications?
  - *Electronic informed consent forms*
  - *Inferencing*
  - …