APPENDIX:

Purpose: The intention of this appendix is to show a real-world use-case deployed at NCSS. The document contains 4 sections, as follows:

1. MODULE I: Clinical Orders Navigator

   Use this module to browse and search different dimensions in the integrated interface, such as the diagnosis (ICD-9 or ICD-10), pharmacy (ATC code), procedure and laboratory. In addition, the module supports end user to find public templates which was defined a set of clinical orders contributed by other researchers. We demonstrate five practical examples, including how to find the clinical orders through full-text search and fuzzy search.

2. MODULE II: Orders Components

   This module can synchronize clinical orders from MODULE I: Clinical Orders Navigator. Many clinical orders are available for defining cohorts. This module supports the end users to know the detail of clinical orders which they selected.

3. Case I: [Osteoporotic Fracture] Incident Case

   In the Case I, we will demonstrate a practical examples of system workflow in the NCSS. First, we introduce how to build a template and adopt the template for
patient identification. Second, we reveal how to use the Report Service that help clarify the characteristics for patient list.

4. **Case II: [Osteoporotic Fracture] exclude malignant neoplasm**

We will continue the results of case 1 and to carry out the process of patient identification in Case II. In this way, you can better understand the advantages of hierarchical structure.

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**MODULE I: Clinical Orders Navigator**

**GOAL**: Design a clinical orders search interface to supports researchers define which orders they want, intuitively. The navigator integrates multiple coding system, such as diagnosis (ICD-9), pharmacy (ATC Code), and laboratory (LOINC).
1. **Clinical Order Type:**

The researcher can choose different clinical order types include diagnosis, drug, laboratory and so on.

2. **Search Mode:**

Two mode can be chose: **Default Mode** and **Template Mode**. If the researcher wants to define a set of clinical orders by himself, he can choose the default mode. In addition, researcher can also use the public templates by choosing template mode which was defined a set of clinical orders contributed by other researchers.

3. **Jump to Template Library:**

If you want to browse which public templates are available, you can click the hyperlink to navigate the **Template Library**.

4. **Query Keywords:**
In order to improve the accuracy and flexibility for clinical orders search, in NCSS, support full text search and fuzzy search with wildcards.

- %: Allows you to match any string of any length
- _: Allows you to match any string of one length

5. **Search Button:**
   To run the search based on the input values of *Query Keywords* and *Clinical Order Type*.

6. **Query Result:**
   Researchers can click the checkbox in the table which presents the search result to decide which clinical orders they selected.

7. **Add Button:**
   Synchronize clinical orders to **MODULE II Orders Components** according to the clinical orders they selected.
Example 1: To retrieval the diagnosis codes for type I and type II diabetes mellitus

- **Case:** fuzzy search with ‘%’
- **Order Type:** Diagnosis
- **Mode:** Default
- **Key Words:** 250%
- **Result:** query result show 40 records

Figure 2. Image of search result for Example 1 in Clinical Orders Navigator
Example 2: To retrieval the diagnosis codes for type I diabetes mellitus

- **Case**: fuzzy search with ‘_'
- **Order Type**: Diagnosis
- **Mode**: Default
- **Key Words**: 250._1
- **Result**: query result show 10 records

![Image of search result for Example 2 in Clinical Orders Navigator](Image)

**Figure 3.** Image of search result for Example 2 in Clinical Orders Navigator
Example 3: To retrieval the drugs that affecting bone structure and mineralization by ATC-Code.

- **Case**: fuzzy search with ‘%’
- **Order Type**: Drug
- **Mode**: Default
- **Key Words**: M058B%
- **Result**: query result show 14 records

| Drug Code | ATC Code | Generic Name | Brand Name (English) | Indications(English) |
|-----------|----------|--------------|----------------------|----------------------|
| A0L1FAE2  | M058A00  | Zoledronic acid | Aclasta 5mg | Inhibitor of osteoclastic bone resorption |
| ARE1FA06  | M058A03  | Pamidronate Disodium | Aredia 15mg | Treats bone metastases of malignant tumors, malignant hypercalcemia and Paget's disease |
| B0N1FA63  | M058A02  | Sodium Clodronate | (DC)Bonefos 300mg | |
| B0N1FA68  | M058A06  | Bisphosphonate Sodium | Boniva 3mg | Treatment of osteoporosis in postmenopausal women |
| B0N4FA83  | M058A02  | Sodium Clodronate | Bonefos 400mg | Treats bone metastases of malignant tumors and malignant hypercalcemia |
| F0S4FAA8  | M058A04  | Alendronate Sodium, Cholecalciferol | (DC)Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men |
| F0S4FA91  | M058A04  | Alendronate Sodium | (DC)Fosamax 70mg | |
| F0S4FA97  | M058A03  | Alendronate Sodium 70mg, Cholecalciferol $600JU | Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men |
| F0S4FA97  | M058A04  | Alendronate Sodium 70mg, Cholecalciferol $800JU | Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men |
| P0M1FA06  | M058A03  | Pamidronate Disodium | Pamisol 15mg | Treats bone metastases of malignant tumors, malignant hypercalcemia and Paget's disease |
| P0R1FA00  | M058A04  | Denosumab | Prolia 60mg | Treats osteoporosis in men and postmenopausal women at high risk for fracture |
| XGE1FA07  | M058A04  | Denosumab | XGEVA 120mg | Prevention of skeletal-related events in patients with bone metastases from solid tumors |
| Z0M1FA05  | M058A06  | Zoledronic Acid | Zometa 4mg | Treats high blood calcium levels and bone damage in patients with cancer |

**Figure 4.** Image of search result for Example 3 in Clinical Orders Navigator
Example 4: To retrieval the drug that indications is osteoporosis

- **Case**: full text search (full-text queries on the text in every column)
- **Order Type**: Drug
- **Mode**: Default
- **Key Words**: Osteoporosis
- **Result**: query result show 16 records

| Drug Code  | ATC Code | Generic Name               | Brand Name (English) | Indications (English)                                                                 |
|------------|----------|----------------------------|---------------------|---------------------------------------------------------------------------------------|
| 1           | 0ON1FA08 | Ibandronate Sodium        | Boniva 3mg          | Treatment of osteoporosis in postmenopausal women                                      |
| 2           | HOS5A01  | Calcitonin, Salmon        | Calcitrol 500U      | Treats bone pain and other symptoms of Paget's disease, Treats osteoporosis and hypercalcemia. |
| 3           | ESF4L27  | Estradiol Valerate        | ESTTRADE 2mg        | Treats symptoms of menopause and lack of estrogen, Prevents osteoporosis after menopause. |
| 4           | ESF4L50  | Conjugated Estrogens      | Estromof 0.025mg    | Treats symptoms of menopause and lack of estrogen, Prevents osteoporosis after menopause. |
| 5           | EBV4LD04 | Estrofore HCl             | Evista 6mg          | Treats and prevents of osteoporosis in postmenopausal women                           |
| 6           | FOR1FA02 | Teriparatide              | BONTEGO 5mg         | Osteoporosis, Men with primary or hypergonadal osteoporosis or postmenopausal women with osteoporosis who are at high risk. |
| 7           | FOR1FA03 | Teriparatide              | Forteo 500mg        | Osteoporosis, Men with primary or hypergonadal osteoporosis or postmenopausal women with osteoporosis who are at high risk. |
| 8           | FOS6FA05 | Alendronate Sodium, Cholecalciferol | (BC) Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men                                      |
| 9           | FOS6FA05 | Alendronate Sodium, Cholecalciferol | (BC) Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men                                      |
| 10          | FOS6FA07 | Alendronate Sodium 70mg, Cholecalciferol 500U | Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men                                      |
| 11          | FOS6FA07 | Alendronate Sodium 70mg, Cholecalciferol 500U | Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men                                      |
| 12          | FOS6FA07 | Alendronate Sodium 70mg, Cholecalciferol 500U | Fosamax Plus | Postmenopausal osteoporosis; Osteoporosis, in men                                      |
| 13          | LAO71F07 | Estradiol                 | LADIL 0.6mg         | Treats symptoms of menopause and lack of estrogen, Prevents osteoporosis after menopause. |
| 14          | MI05FA06 | Calcitonin, Salmon        | Micractin 200U      | Treatment of osteoporosis in postmenopausal women                                      |
| 15          | OSE5LF07 | Estradiol                 | Oestrogel 0.6mg     | Treats symptoms of menopause and lack of estrogen, Prevents osteoporosis after menopause. |
| 16          | PRO1FA00 | Denosumab                 | Prola 60mg          | Treats osteoporosis in men and postmenopausal women at high risk for fracture           |

**Figure 5.** Image of search result for Example 4 in Clinical Orders Navigator
Example 5: To find the template of Charlson Comorbidity Index

- **Case**: fuzzy search with ‘%’
- **Order Type**: Diagnosis
- **Mode**: Template
- **Key Words**: CCI%
- **Result**: query result show 1 records

![Image of search result for Example 5 in Clinical Orders Navigator](image)

**Further Explain:**

1. When the researcher selected the Template mode and entered the keyword-“CCI%” and then the Clinical Orders Navigator will search from the Template Library.
2. The search results found a record of the CCI (Charlson Comorbidity Index).
   The researcher can click the label (blue text) and then it will pop-up a window to show the detail about all orders in the template.
3. The researcher can click the “Use Template” button and it will synchronize all clinical orders to MODULE II: Orders Components from this template.
MODULE II: Orders Components

**GOAL**: Design a component to record clinical orders which was defined by researchers, and the clinical orders will synchronize to the component from MODULE I: Clinical Orders Navigator.

![Image of Charlson Comorbidity Index by Orders Components](image)

**Figure 7.** Image of Charlson Comorbidity Index by Orders Components

1. **Clinical Order Type:**
   To record the current clinical order type, such as pharmacy and laboratory.

2. **Order Detail:**
   To record uniquely identifies and description for each clinical order. For example, if the clinical order type is diagnosis, it will record the ICD-9 code and its description.

3. **Category:**
   Module II provide a way to help researchers designing a series of categories, because most of the clinical orders were in a collection.

4. **Score:**
   If you want to give a weight to the clinical orders to calculate some indicators, like
CCI (Charlson Comorbidity Index), and then you can fill in a score based on the literature or guideline. The field is not required.

5. **Export to Excel:**

Because of **Criteria Components** store clinical domain knowledge, we also implement some batch function, such as export/import form Excel that allow researchers to process batch insert, update and export those criteria, easily.
Case I: [Osteoporotic Fracture] Incident Case

**GOAL:** Find the patients diagnosed with hip or vertebral fractures and age greater than 50 years old between 2010/01/01 and 2014/12/31. We based on workflow to introduce each stage, as depicted in Figure 10.

![Figure 8. System workflow of NCSS.](image)

**Stage 1: Build Template**

**GOAL:** Design a process to create templates for recording clinical orders and categories which based on specific guidelines or research. For example, such as hip or vertebral fractures, including ICD-9-codes 820, 805, and 806 and we cited the guideline to build a template, as depicted in Figure 11.
Figure 9. Build a template for recording diagnosis codes and guideline.

1. **Basic Setting:**
   - **Label:** diagnosed with a hip or vertebral fracture
   - **Share Template:** Yes
   - **Reference 1:** Cosman, F., et al., Clinician’s guide to prevention and treatment of osteoporosis. Osteoporosis international, 2014. 25(10): p. 2359-2381.
- **Reference 2**: Compston, J., et al., Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas, 2009. 62(2): p. 105-108.

- **Reference 3**: Orimo, H., et al., Japanese 2011 guidelines for prevention and treatment of osteoporosis—executive summary. Archives of osteoporosis, 2012. 7(1-2): p. 3-20.

2. **Orders Components**:

   - **Clinical Order Type**: Diagnosis
   - **Order Detail**: There are 96 ICD-9-codes including 820, 805, and 806.
   - **Category**: ICD-9-codes with 805 and 806 set “Fracture” as a category and ICD-9-codes with 820 set “hip” as a category.
   - **Score**: not required. (If you want to give a weight to the clinical orders to calculate some indicators, like CCI (Charlson Comorbidity Index), and then you can fill in a score based on the literature or guideline. The field is not required. More detail please refer to the **MODULE II: Orders Components** on page 10.)

3. **Clinical Orders Navigator**:

   - **Order Type**: Diagnosis
   - **Key Words**: ICD-9-codes including 820, 805, and 806.

More detail please refer to the **MODULE I: Clinical Orders Navigator** on page 3.
Stage 2: Patient Identification

**GOAL:** The stage of Patient identification, which is the matching of the clinical needs to find the patient list. This example demonstrated how to use the template as clinical orders.
Identification

1. **Basic Setting:**

   To define the surveillance topic, and set up the duration of observation from a particular data source, such as outpatient, admission, and emergency.
   - **Label:** [Osteoporotic Fracture] Incident Case
   - **Branch:** Taipei main hospital
   - **Patient source:** outpatient, admission and emergency
   - **Start date:** 2009/01/01
   - **End date:** 2014/12/31

2. **Clinical Orders Navigator:**

   - **Case:** full text search with ‘Hip or vertebral fracture ’
   - **Order Type:** Diagnosis
   - **Mode:** Template
   - **Key Words:** Hip or vertebral fracture
   - **Result:** query result show 1 records

3. **Use Template:**

   If you click the ‘Use Template’ button, this template will synchronize to the orders component. There synchronized 96 diagnosis codes in order setting.

4. **Order Setting:**

   There are two criteria: First, researchers define the 96 diagnosis codes which have been synchronized to the Orders Component. Second, filtering the age between 50 to 130.

**REC, Cloud Batch Process and Data Mart**
The setting of case “[Osteoporotic Fracture] Incident Case” had been authorized, it was been added a task to Task Queue for cloud batch process in server side. The cloud batch process maintains a Task Queue. Every task will be executed follow First-In-First-Out (FIFO) mechanism in batch server that read the setting of Identification to query eligible patients in IMDB. After completion of the task, the patient list will be stored into database and send a mail notification to researchers. Finally, the case’s status become “Finished” in Data Mart.

| ID | Status | Label                                           | Duration         | Request Date   | Remark | Setting | Report |
|----|--------|------------------------------------------------|------------------|----------------|--------|---------|--------|
| 73 | Finished| [Osteoporotic Fracture] Incident Case           | 1/1/2010 - 12/31/2014 | 7/19/2017      |        |         |        |

**Figure 21.** List the case 73 had been identified in Data Mart.

**Report Service**

1. **View of Characteristics:**

   The view is demographic summary that help clarify the characteristics for patient list. For example, the descriptive statistics of age, gender, body mass index (BMI), income level, as show as figure 12.
Figure 12. View of characteristics in Case I

2. **View of Longitudinal Incidence Trend:**

The view presents the incidence trend by time series chart and provides a real-time interactive query by time interval, including monthly, quarterly, or yearly, as shown in figure 13.
3. **View of Source Record:**

The view present number of include/exclude patients in every Identification process. If the patient list contains hierarchical structure that run the process of identification more than once, the Report Service can track all result of identification in aggregation table, as show as figure 14.

![Figure 14. View of Source Record in Case I](image)
Case II: [Osteoporotic Fracture] excluding malignant neoplasm

**GOAL:** To exclude patients diagnosed with malignant neoplasm within 1 year before index fracture from the patient list based on case 73. This example does not show a similar process; thus, we only demonstrated the Identification process and Report Service. We designed a mechanism for reusing the patient list in the Data Mart. We believe that this identified list of patients should be reused, especially for the design of subgroup study, case control study, or research on a similar context. To better interpret the identification process of each patient list, we designed a hierarchical structure, using which each patient list could be traced back to its patient data source and researchers could compare every patient data source with the characteristics and longitudinal incidence trend in the Report Service. We aimed to describe the advantages of the hierarchical structure, and compare the differences between Cases I and II.
Figure 35. An electronic form for recording the setting of patient identification

1. **Basic Setting:**
   - **Label:** [Osteoporotic Fracture] exclude malignant neoplasm
   - **Patient list:** [Osteoporotic Fracture] incident case (case number 73). We designed a mechanism for reusing the patient list in Data Mart, using which researchers could select a patient list from the drop-down list as patient data source for patient identification process.

Figure 46. A patient list from the drop-down list as patient data source

   - **Order type:** Diagnosis
   - **Patient source:** outpatient, admission and emergency
   - **Start date:** 2009/01/01
   - **End date:** 2014/12/31

2. **Clinical Orders Navigator:**
   - **Case:** full text search with ‘malignant neoplasm’
   - **Order Type:** Diagnosis
   - **Mode:** Template
Key Words: malignant neoplasm

Result: query result show 1 record

3. **Use Template:**

If you click the ‘Use Template’ button, this template will synchronize to the orders component. There synchronized 586 diagnosis codes in order setting.

5. **Order Setting:**

There are two criteria: First, researchers define the 586 diagnosis codes which have been synchronized to the Orders Component and every diagnosis code have 2 status - NOT and before 365 day.

- Include / Exclude : NOT
- Limitation of index : before 365 day

The patient will be excluded when he/she is diagnosed with a malignant neoplasm within one year before the index date (newly diagnosed with a hip or vertebral fracture) by the Cloud Batch Process.

**Report Service**

1. **Characteristics view:**

The characteristics view implies the demographic summary of the characteristics that helps clarify them for a patient list. For the case “[Osteoporotic Fracture] excluding malignant neoplasm”, we can realize the descriptive statistics of age, gender, body mass index (BMI), income level, as show in Figure 17. Further, the results of Case 1 can be compared with those in Figure 12 to understand that the number of males decreased from 1,583 to 1,356, while the number of females decreased from 3,115 to 2,785.
Case II has a hierarchical structure, using which each patient list could be traced back to its patient data source. Figure 15 shows two patient lists: Case I “[Osteoporotic Fracture] Incident Case (73)” and Case II “[Osteoporotic Fracture] excluding malignant neoplasm”.

The end user could compare every patient list by using the longitudinal incidence trend at specific intervals such as monthly, quarterly, and yearly. We compared Cases I and II quarterly with respect to the Longitudinal Incidence Trend view and stratified them based on gender, as shown in Figure 18.
Figure 18. Compare with Case I and Case II in View of Longitudinal Incidence Trend by Quarterly and stratified by gender.

3. **Source Record view:**

Here, we describe the advantages of the hierarchical structure in the Source Record view. As Case II contains a hierarchical structure that runs the process of identification more than once, the Report Service can track all the results of identification in the aggregation table. Finally, we can obtain a source record report. The Source Record view presents the number of patients included/excluded in every Identification process, as shown in Figure 19.

![Source Record view](image)

**Figure 19.** View of Source Record in case II

Finally, a cohort study flow was developed based on the results (Figure 20).
Figure 20. A cohort study flow based on the results of Case II