**Chapter 6 – Formalized Learning -- Research**

**Introduction**

In previous chapters the algorithms needed to organize the essential data (ideas) have been discussed with respect to selecting vocabulary, subsets of ideas, and organizing those using the research design template. This chapter brings together the elements to develop an algorithmically supported formal approach to learning with the intent to extend the existing knowledge and to develop new.

The approach has a successful history in clinical trial research. Assume that a new treatment is introduced. How should this be studied if the intent is to develop a transparent path of evidence dealing with the action of the treatment alone and in combination with others? There are obvious first questions:

1. What is the acceptable dose of the new in minimizing adverse effects and in possibly showing positive effects? Do these effects differ in individuals with different diseases and/or severity of illness?
2. What is the optimal dose of the new in effecting positive results? Are the beneficial effects uniformly observed in individuals with different diseases and/or degrees of severity of disease?
3. What are the short, intermediate, and long term effects of treatment with this new agent? Are there subgroups of individuals who show different adverse or beneficial results?

The subsequent questions include:

1. W hat are the adverse and beneficial effects of the new agent when combined with more established treatments? Are there differences in subgroups of individuals with differing disease presentations and/or degree of severity?
2. Are there particular combinations of agents that offer more beneficial results? Are there subgroups of patients who show more beneficial results?

These questions often are addressed by individual studies performed by a large number of different investigators. In addition to the specific information acquired, there is evidence of how the new agent performs in different environments and situations.

This body of preliminary evidence can then be used to develop research protocols testing the ‘best’ combinations of treatment agents in the most susceptible subgroups. Those findings will establish a new body of knowledge dealing with the treatment of the particular disease(s) and the results of wide spread application can be determined.

The values of this learning experience are: transparency of process, documentation of problems and benefits, and formalized documentation of the experiences associated with each study. It is essential in developing background when, ***in fact***, there is no information available in the published literature.

The fact that research is performed by an elite subset of the individuals specializing in a subject means that shortcuts are practiced. The most notable of these is the selection of the problem to be studied. With specialists, that choice is an ‘obvious’ one. To the student, the choice could be a mystery.

A more usual situation involves an abundance of previous publications and the need to explore those in order to find gaps and/or inconsistencies. This situation has involved personal, private procedures in identifying, extracting, and organizing information. As a result, the quality of the process is questionable because it is not transparent. The development of the research problem can be better understood if the formalized process employing ideas and algorithms is used. The time involved is considerably less than using traditional procedures and decidedly more transparent. The process involves the following tasks:

1. Organize the terms used in the ideas – most frequent to least frequent.
2. Select high frequency terms (***direct)*** that also are specific to the topic.
3. Identify terms (potentially ***indirect***) linked to each of the direct terms.
4. Build a matrix of direct terms and their associated terms.
5. Identify indirect terms that occurred with higher ***consistency*** across the direct set.
6. Identify terms (***associated***) linked to each of the indirect terms.
7. Build a matrix of indirect terms and their associated terms.
8. Determine the ***frequency*** and ***consistency*** of use of these associated terms.
9. Build an idea map showing the direct, indirect, and highest frequency associated terms.
10. Use that map to build different research designs using the research design template.
11. Determine measures to use in describing and evaluating each design.
12. Array those designs from ‘best’ to ‘less’ using those measures.
13. Translate the ‘best’ design into a protocol.

**Tasks**

**Organize Terms in Ideas:** The vocabulary used by authors can be organized with respect to the ***frequency*** of each used in ideas. Table 1 shows an excerpt of this vocabulary array. These terms are from the site – <http://researchdogdiseases.com>. There were over 3 million ideas identified with dog ideas totaling over 200,000. The higher frequency terms forming ideas included diseases – infection and cancer – and ***no specific treatments***. The lack of emphasis on treatments in the higher frequency ideas may indicate a lack of evidenced-based management of dog diseases.

**Table 1. Frequency of Terms in Ideas.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Term** | **Total** | **Term** | **Total** | **Term** | **Total** | **Term** | **Total** |
| Total Ideas | 3029428 |  |  |  |  |  |  |
| dog | 237235 | animal | 31831 | lesion | 17971 | chemical | 13285 |
| cell | 57704 | blood | 27170 | induce | 16570 | health | 13061 |
| disease | 56596 | tumor | 23050 | breed | 15669 | abnormal | 13013 |
| canine | 54367 | protein | 22396 | antigen | 15620 | histologic | 12592 |
| clinic | 52023 | amine | 20973 | radiograph | 13942 | **Etc**. |  |
| infect | 47754 | virus | 20153 | chronic | 13637 |  |  |
| normal | 36342 | diagnosis | 18186 | antibodies | 13340 |  |  |
| infection | 34211 | response | 18112 | fusion | 13334 |  |  |

The next task involves separating these high frequency terms into two sets – those that provide specific meaning relative to the topic (dog disease) and those that are more general in meaning.

Table 2 shows a subset of those ***specific meaning higher frequency*** terms. In this example, dog would be described by core terms – infect, virus, tumor, and response. While other terms would expand on this basic description, these offer a first step.

**Table 2. High Frequency Specific Terms.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Term** | | **Infect** | **Tumor** | **Virus** | **Response** | **Sum** |
| Grand sum | 84157 | | 22270 | 28657 | 17721 | 152805 |
| dog | 8427 | | 2042 | 1696 | 1593 | 13758 |
| infect | 7105 | | 24 | 1160 | 279 | 8568 |
| response | 474 | | 183 | 112 | 0 | 769 |
| tumor | 51 | | 24 | 36 | 181 | 292 |
| virus | 1543 | | 29 | 1513 | 84 | 3169 |

Table 3 shows an excerpt from the ***higher frequency and more general*** terms linked with dog. These terms may play a role in describing dog disease but in a more indirect way. As such, their links with the direct terms is the next task to determine. Terms providing general information (e.g., disease, clinic, or canine) may describe a backdrop or milieu in which the specific term-ideas could provide actions. By separating the more specific from the more general, ideas can be used to build more active relationships. The specific-meaning ideas aid in developing possible interventional studies. In this way the research scene is moved from description to intervention.

**Table 3. High Frequency General Terms.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Term** | **Dog** | **Infect** | **Tumor** | **Virus** | **Response** | **Sum** |
| disease | 5510 | 1782 | 195 | 493 | 261 | 8241 |
| clinic | 5708 | 1376 | 307 | 192 | 379 | 7962 |
| canine | 2554 | 1608 | 803 | 2169 | 250 | 7384 |
| cell | 2966 | 920 | 1481 | 533 | 467 | 6367 |
| animal | 3002 | 1253 | 177 | 297 | 177 | 4906 |
| normal | 3650 | 247 | 255 | 38 | 232 | 4422 |
| blood | 2514 | 553 | 115 | 81 | 154 | 3417 |
| breed | 2621 | 168 | 60 | 39 | 49 | 2937 |
| amine | 2054 | 402 | 114 | 130 | 152 | 2852 |
| health | 2155 | 325 | 39 | 80 | 55 | 2654 |
| antigen | 1043 | 643 | 97 | 396 | 200 | 2379 |
| protein | 1365 | 342 | 166 | 349 | 134 | 2356 |

Identification of potentially ***indirect terms involves primarily consistency*** of use of the term across different direct terms and only secondarily, frequency of occurrence. Again, possible terms are separated by specificity of meaning. Table 4 shows the consistent terms (row labels) that also have more specific meaning.

**Table 4. Consistent, Specific Terms That May Serve as Indirect in Describing Dog Disease.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Term** | **Dog** | **Infect** | **Tumor** | **Virus** | **Response** | **Sum** |
| coronary | 774 | 2 | 0 | 1 | 78 | 855 |
| larvae | 168 | 261 | 0 | 6 | 10 | 445 |
| flea | 355 | 73 | 0 | 1 | 13 | 442 |
| allergen | 318 | 13 | 0 | 2 | 57 | 390 |
| diabetic | 345 | 12 | 5 | 0 | 13 | 375 |
| remission | 278 | 8 | 39 | 0 | 42 | 367 |
| metastasis | 203 | 7 | 141 | 0 | 7 | 358 |

Table 5 shows an excerpt of the consistent but general meaning terms. They would be passed over in selecting indirect terms but may be used in further describing the idea structure involving direct, indirect, and associated terms. ***Occlusion*** is included in Table 5 and illustrates a classification difficulty. The term could be considered to be specific in certain settings and general in others. This example illustrates a more critical problem. Namely, the information provided by a single word versus that provided by an idea involving that word. Ideas tend to clarify the meaning and as such, facilitate classification of terms as general vs. specific.

**Table 5. Consistent, General Terms.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Term** | **Dog** | **Infect** | **Tumor** | **Virus** | **Response** | **Sum** |
| caninum | 312 | 371 | 0 | 9 | 6 | 698 |
| occlusion | 558 | 15 | 2 | 0 | 55 | 630 |
| atopic | 521 | 27 | 0 | 4 | 53 | 605 |
| egg | 279 | 180 | 0 | 11 | 5 | 475 |
| arterial | 379 | 23 | 9 | 0 | 39 | 450 |
| gibsoni | 177 | 257 | 0 | 4 | 10 | 448 |
| lameness | 405 | 20 | 5 | 0 | 9 | 439 |
| dosage | 319 | 42 | 20 | 0 | 24 | 405 |
| adrenal | 291 | 9 | 64 | 0 | 38 | 402 |

**Table 6. Direct and Indirect Terms in a Matrix.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Term** | **Coronary** | **Larvae** | **Flea** | **Allergen** | **Diabetic** | **Remission** | **Metastases** | **Sum** | **Consist** |
| dog | 775 | 226 | 355 | 327 | 620 | 278 | 382 | 2963 | 7 |
| infect | 1 | 227 | 46 | 6 | 11 | 4 | 4 | 299 | 7 |
| response | 78 | 14 | 13 | 60 | 28 | 42 | 10 | 245 | 7 |
| tumor | 0 | 0 | 0 | 0 | 14 | 39 | 241 | 294 | 3 |

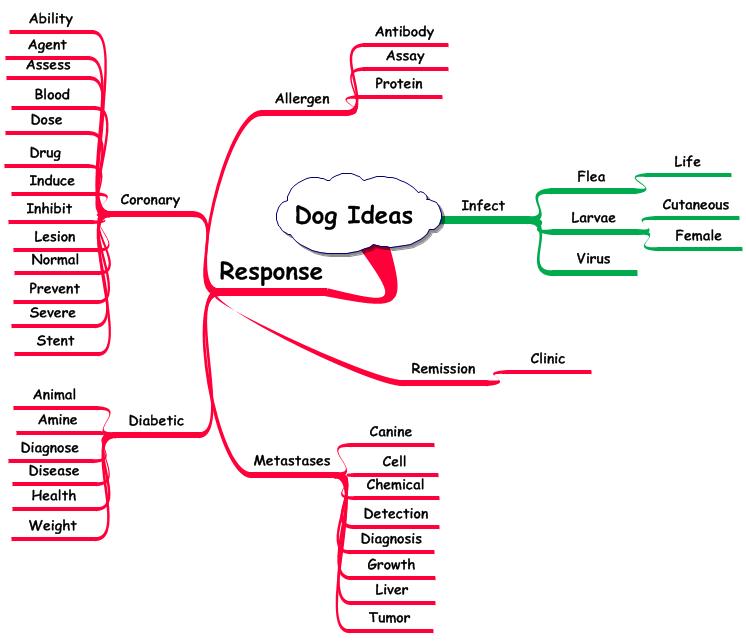
Table 6 shows the links between the direct terms (row headings) and the indirect ones (column headings). The consistency of use also is shown in the final column.

Table 7 shows the other terms associated with the indirect ones. The selection criterion was a consistency of 7. The highest frequency idea for each indirect-associated term combination is highlighted in red. As the total occurrence of the idea reduces, the frequent idea becomes less obvious with duplicates and triplets showing the same low frequencies.

**Table 7. Associated Terms Linked with Indirect Terms.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Term** | **Corornary** | **Larvae** | **Flea** | **Allergen** | **Diabetic** | **Remission** | **Metastases** |
| Grand Sum | 9872 | 2794 | 2094 | 3330 | 4306 | 1674 | 3655 |
| blood | **365** | 21 | 20 | 11 | 73 | 6 | 5 |
| disease | 78 | 26 | 31 | 77 | **101** | 45 | 52 |
| clinic | 22 | 17 | 29 | 67 | 83 | **85** | 50 |
| animal | 68 | 25 | 52 | 49 | **84** | 9 | 23 |
| induce | **198** | 6 | 10 | 25 | 29 | 27 | 6 |
| amine | **105** | 30 | 21 | 41 | 67 | 3 | 18 |
| canine | 66 | 20 | 15 | 43 | 62 | 11 | **68** |
| cell | 30 | 8 | 12 | 24 | **51** | 29 | 94 |
| normal | **102** | 5 | 7 | 15 | 69 | 17 | 19 |

**Figure 1. Higher Frequency Ideas Linked with Dog.**

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The idea map in Figure 1 shows the higher frequency terms all linked with the central term – dog – as well as to direct and indirect terms forming the idea structure. In this map, the direct idea – dog & response – forms a basis for expansion of indirect and associated terms.

**Response Related Ideas**

The response ideas were further explored by classifying them into dimensions representing components of the relationship between – dog & response. The dimensions were:

1. Personal Factors – those variables describing the study participants.
2. Subject Factors – those variables describing the topic. Sub-dimensions included:
   1. Chemicals
   2. Pathogens
   3. Cancers
   4. Tissues
   5. Immune
3. Treatment Factors – those variables describing the types of interventions.
4. Outcome Factors – those variables describing the interactions between interventions and subject factors.
5. Method Factors – those variables describing procedures used.

Tables 8A – 8J show excerpts from the different dimensions. The higher frequency terms are shown. The idea – dog & response – occurred 1593 times. In contrast, the idea – puppies & response – was used 20 times.

**Table 8A – Higher Frequency Terms Linked**

**with the Central Term – Response: Personal Factors.**

|  |  |
| --- | --- |
| **Term** | **Personal** |
| dog | 1593 |
| canine | 250 |
| animal | 177 |
| breed | 49 |
| weight | 35 |
| infant | 32 |
| beagle | 26 |
| parent | 24 |
| puppies | 20 |

**Table 8B – Higher Frequency Terms Linked**

**with the Central Term – Response: Subject Factors**

|  |  |
| --- | --- |
| **Term** | **Subject** |
| disease | 261 |
| humoral | 114 |
| chronic | 101 |
| occlusion | 55 |
| agent | 53 |
| proliferative | 44 |
| distemper | 39 |
| stress | 38 |

**Table 8C – Higher Frequency Terms Linked**

**with the Central Term – Response: Cancers**

|  |  |
| --- | --- |
| **Term** | **Cancer** |
| lymphoma | 34 |
| cancer | 33 |
| sarcoma | 16 |
| melanoma | 16 |
| necrosis | 12 |
| neoplasm | 12 |

**Table 8D – Higher Frequency Terms Linked**

**with the Central Term – Response: Immune**

|  |  |
| --- | --- |
| **Term** | **Immune** |
| infect | 279 |
| antibody | 214 |
| antigen | 200 |
| inflammatory | 167 |
| allergen | 57 |
| mitogen | 57 |
| antibodies | 54 |
| immunologic | 53 |

**Table 8E – Higher Frequency Terms Linked**

**with the Central Term – Response: Chemical**

|  |  |
| --- | --- |
| **Term** | **Chemical** |
| hormone | 74 |
| choline | 51 |
| acid | 50 |
| cytokine | 45 |
| enzyme | 42 |
| proteins | 41 |
| adenosine | 41 |
| histamine | 40 |
| cortisol | 38 |

**Table 8F – Higher Frequency Terms Linked**

**with the Central Term – Response: Pathogen**

|  |  |
| --- | --- |
| **Term** | **Pathogen** |
| virus | 84 |
| parasite | 65 |
| pathogen | 52 |
| leishmania | 45 |
| cdv | 44 |
| canis | 34 |

**Table 8G – Higher Frequency Terms Linked**

**with the Central Term – Response: Tissue**

|  |  |
| --- | --- |
| **Term** | **Tissue** |
| cell | 467 |
| tumor | 181 |
| blood | 154 |
| lymphocyte | 111 |
| coronary | 78 |
| platelet | 76 |
| vascular | 63 |
| lesion | 59 |
| thyroid | 59 |
| brain | 57 |

**Table 8H – Higher Frequency Terms Linked**

**with the Central Term – Response: Treatment**

|  |  |
| --- | --- |
| **Term** | **Treatment** |
| clinic | 379 |
| dose | 195 |
| induce | 181 |
| vaccine | 98 |
| drug | 86 |
| vaccination | 71 |
| chemotherapy | 68 |
| stent | 63 |
| radiation | 47 |

**Table 8I – Higher Frequency Terms Linked**

**with the Central Term – Response: Outcome**

|  |  |
| --- | --- |
| **Term** | **Outcome** |
| immune | 523 |
| normal | 232 |
| inhibit | 102 |
| life | 98 |
| abnormal | 64 |
| survival | 61 |
| health | 55 |
| severe | 52 |

**Table 8J – Higher Frequency Terms Linked**

**with the Central Term – Response: Methods**

|  |  |
| --- | --- |
| **Term** | **Method** |
| assess | 119 |
| diagnosis | 76 |
| assay | 64 |
| ability | 58 |
| atopic | 53 |
| pathologic | 52 |
| analysis | 48 |
| histologic | 41 |

**How Authors Used Response Ideas**

Exhibit 1 shows sentences from a 2009 document that illustrates how the authors used ideas from the Cancer, Treatment, and Outcome dimensions. The ideas of interest were:

**CANCER TREATMENT OUTCOME**

**lymphoma clinic response**

**Hodgkin’s chemotherapy relapse**

**Exhibit 1. Sentences and Highlighted Terms Linked with Response – PMID 19999354.**

**Source:** [**Lawrence J**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Lawrence%20J%5BAuthor%5D&cauthor=true&cauthor_uid=19999354)**1,** [**Vanderhoek M**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Vanderhoek%20M%5BAuthor%5D&cauthor=true&cauthor_uid=19999354)**,** [**Barbee D**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Barbee%20D%5BAuthor%5D&cauthor=true&cauthor_uid=19999354)**,** [**Jeraj R**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Jeraj%20R%5BAuthor%5D&cauthor=true&cauthor_uid=19999354)**,** [**Tumas DB**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Tumas%20DB%5BAuthor%5D&cauthor=true&cauthor_uid=19999354)**,** [**Vail DM**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Vail%20DM%5BAuthor%5D&cauthor=true&cauthor_uid=19999354)**. Use of 3'-deoxy-3'-[18F]fluorothymidine PET/CT for evaluating response to cytotoxic chemotherapy in dogs with non-Hodgkin's lymphoma.** [**Vet Radiol Ultrasound.**](http://www.ncbi.nlm.nih.gov/pubmed/?term=19999354) **2009 Nov-Dec;50(6):660-8 PMID: 19999354**

***Sentence 2: We evaluated prospectively the proliferation marker 3'-deoxy-3'[18F] fluorothymidine (FLT) in the context of FLT-PET/CT for detection of early response, confirmation of posttreatment response, and prediction of relapse in dogs with non-Hodgkin's lymphoma.***

***Sentence 19: FLT-PET/CT functional and anatomical imaging shows promise for the evaluation of response to cytotoxic chemotherapy in dogs with non-Hodgkin's lymphoma and for predicting relapse before standard clinical and clinicopathologic confirmation.***

**Exhibit 2. Sentences and Highlighted Terms Linked with Response – PMID 15835237.**

***Source:*** [***Wiedemann AL***](http://www.ncbi.nlm.nih.gov/pubmed/?term=Wiedemann%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=15835237)***1,*** [***Charney SC***](http://www.ncbi.nlm.nih.gov/pubmed/?term=Charney%20SC%5BAuthor%5D&cauthor=true&cauthor_uid=15835237)***,*** [***Barger AM***](http://www.ncbi.nlm.nih.gov/pubmed/?term=Barger%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=15835237)***,*** [***Schaeffer DJ***](http://www.ncbi.nlm.nih.gov/pubmed/?term=Schaeffer%20DJ%5BAuthor%5D&cauthor=true&cauthor_uid=15835237)***,*** [***Kitchell BE***](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kitchell%20BE%5BAuthor%5D&cauthor=true&cauthor_uid=15835237)***. Assessment of corticosteroid-induced alkaline phosphatase as a prognostic indicator in canine lymphoma.*** [***J Small Anim Pract.***](http://www.ncbi.nlm.nih.gov/pubmed/?term=15835237) ***2005 Apr;46(4):185-90. PMID: 15835237***

***Sentence 6: It was found that sALP is not a useful prognostic indicator for response rate and remission duration in dogs with lymphoma.***

Exhibit 2 shows another example of authors’ use of the response ideas. That sentence linked terms from **Personal 🡪 Cancer 🡪 Outcome** dimensions.

**Melanoma, Vaccine, Response Ideas:** Table 9 shows the history of studies reporting a relationship between melanoma (Cancer Dimension), vaccine (Treatment Dimension), and response (Outcome Dimension). The earliest study was entered into PubMed in 1999 and the latest in 2014. The table reports the two primary reference elements – the source data (journal publication date and identifiers) and the PubMed Identification number (Ident). The latter is the most efficient for retrieval of specific documents.

**Table 9. Studies Considering the Relationship between Melanoma, Vaccine, Response in Dogs.**

|  |  |
| --- | --- |
| **Source** | **Ident** |
| [Cancer Gene Ther. 1999 Jan-Feb;6(1):26-36.](http://www.ncbi.nlm.nih.gov/pubmed/10078961) | 10078961 |
| [Clin Cancer Res. 2003 Apr;9(4):1284-90.](http://www.ncbi.nlm.nih.gov/pubmed/12684396) | 12684396 |
| J Vet Intern Med. 2005 Jan-Feb;19(1):56-63. | 15715049 |
| Cancer Immunol Immunother. 2006 Apr;55(4):433-42. | 15965647 |
| Cancer Gene Ther. 2006 Oct;13(10):905-18. | 16710345 |
| Mol Ther. 2007 Nov;15(11):2044-50. | 17726460 |
| Am J Vet Res. 2011 Dec;72(12):1631-8. doi: 10.2460/ajvr.72.12.1631. | 22126691 |
| Vet J. 2013 Oct;198(1):28-33. doi: 10.1016/j.tvjl.2013.06.005. | 23850019 |
| Clin Cancer Res. 2014 Jul 15;20(14):3753-62. doi: 10.1158/1078-0432.CCR-13-3042. | 24874834 |
| Expert Opin Biol Ther. 2014 Oct;14(10):1427-42. doi: 10.1517/14712598.2014.927433. | 25023219 |

**Protocol Development**

The research design template provides an outline of the elements needed in developing a plan of conduct (i.e., protocol). The template approach can be employed to develop and evaluate various research strategies. As such, it is useful in the cognitive process leading to effective generation of new knowledge. It is a form of simulation enabling the analyst to visualize the system that will be transformed into specific procedures by the construction of the research protocol. That outline is:

1. ***Recruitment of study participants***. The Personal Dimension provides the details needed in describing the participants. Mechanisms to accomplish recruitment of potentially eligible individuals need to be developed.
2. ***Establishment of Eligibility***. The Subject Dimension provides the details needed in determining the entry status of each participant.
3. ***Assignment to Treatment***. The Treatment Dimension provides the details needed in assigning study participants to the treatments being studied.
4. ***Selecting Outcomes***. The Outcome Dimension provides the details needed in determining the effects of the treatments.
5. ***Selecting Methods***. The Methods Dimension provides the details needed in choosing the methods used in recruitment, eligibility, treatment, and outcome.

The central database and the higher cognitive function algorithms create a different type of expert. Traditionally, a specialist would be chosen for his/her wisdom and opinions. With the tools described above, the expert is needed to clarify and expand the higher cognitive functions while the more clerical/mechanical ones are converted to a transparent, evidence-based system. By making the analysis transparent and quality-controlled, the needed documentation is readily available. This facilitates the shift to true intellectual prowess by the expert. In a similar fashion, the student, new to the subject, can begin learning by solving problems and by building new idea structures. The ability to acquire, organize, and utilize the ideas enhances the transformation from novice to professional. The need to spend long hours in the library stacks is replaced by a need to spend time thinking and researching. Those actions could yield an operational description of critical and creative thinking.