# Investigational Agents and Regimens That Are Also Commercially Available: Instructions for Building “Possible Side Effects” Tables (Risk Lists) for Informed Consent Forms

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Note to informed consent form authors: There are many references that can provide reliable and accurate adverse event risk profiles for anticancer agents and regimens. The following instructions are general procedures the NCI developed and utilizes for building its Tables of Possible Side Effects (risk lists) for commercial anticancer agents and regimens. Depending on an organization’s circumstances or needs, modified procedures or other processes may be more suitable or used. In 2021, upon recommendations by the CTEP Pharmaceutical Management Branch at NCI, the NCI began to rely primarily on the most recent FDA package insert to collate potential adverse events for each anticancer agent. Other sources, including online pharmaceutical databases such as Lexicomp and Micromedex, physicians, pharmacists, patient advocates, Informed Consent Working Group Members, and scientific publications, will continue to be used as needed. Prior to 2021, the NCI largely collated adverse event risk profiles principally from the Micromedex database, after an initial review of many sources (1).

The adverse events included in these references are listed using scientific terms that are not appropriate for the target patient audience reading informed consent documents. The NCI developed a systematic approach to translate scientific adverse event terms to lay language. A library of scientific terms was translated to lay language based on a review of over 90 commonly used chemotherapy agents. This library is periodically revised and updated as additional scientific adverse events are documented for each agent. A copy of the library file (*NCI* Risk Term Library) is available in the CTEP-Supported Trial Resources section of the DCTD website.

After translating the scientific terms into lay terms appropriate for informed consent documents, “possible side effects” documents are developed and updated by sorting the informed consent terms into tables based on severity and frequency of occurrence. The informed consent terms, formats, and standard language were created with input from a variety of sources, including physicians, pharmacists, patient advocates, and the Informed Consent Working Group for Risks (2-7). The informed consent terms used in the risk lists are intended to be generally consistent with the CTCAE translated informed consent terms for investigational agents.

Procedure for developing or updating a single commercially available anticancer agent risk list:

1. For a single anticancer agent, associated scientific adverse events are identified using the most recent FDA package insert and/or other sources (as noted above).
2. The *NCI Risk Term Library* is consulted and each scientific adverse event is translated into an informed consent term. Some adverse events are conditions, such as ‘Reversible Posterior Leukoencephalopathy Syndrome.’ For these conditions, the *NCI Risk Term Library* includes a list of symptoms to be included in the risk lists.
3. Generally, the language used in the risk lists will be formatted with the translated informed consent term followed by “which may cause” and a list of symptoms (if applicable).
	1. Example: “abnormal heartbeat which may cause fainting”
4. In cases in which different scientific adverse events are translated into similar informed consent terms and/or symptoms, the *NCI Risk Term Library* also provides “directions” in order to suggest a consistent approach for avoiding redundancy when translating terms for the risk lists without losing important potential risk information for patients.
5. Some scientific adverse event terms have symptoms that should always be listed with the informed consent term. The *NCI Risk Term Library* will indicate in the “directions” which symptoms cannot be omitted.
	1. Example: in the risk lists, the adverse event, Allergic Reaction, will always be listed as “Allergies which may cause hives, low blood pressure, wheezing, or shortness of breath”.
6. All appropriately de-duplicated, relevant adverse event informed consent terms should be included in the risk list and categorized under the appropriate frequency category. There are three frequency categories- ‘Common, Some May Be Serious’ (frequency greater than 20%),’ ‘Occasional, Some May Be Serious’ (frequency between 4 and 20%),’ and ‘Rare, and Serious’ (frequency less than 4%).
	1. For some possible side effects, a percentage is also given. When available, the upper limit of the percentage range listed should be used to determine the frequency category. In the absence of a percentage in the FDA package insert, a review of other reference sources (e.g., Lexicomp or Micromedex) may be consulted to make a suggested determination how to categorize side effects within the table.
7. If the duplicative informed consent terms and/or symptoms are translated from scientific adverse events occurring with different frequencies, the term should be removed from the less frequent category and placed in a more frequent category in the risk list.
8. If the two different scientific adverse events are translated into a primary informed consent term and as a symptom associated with another condition, the symptom should be omitted (unless the “directions” indicate an exception) and the primary informed consent term should be listed, even if it is categorized as occurring less frequently.
	1. Example: If “High blood pressure which may cause headaches, tiredness, blurred vision” is listed in the ‘Common, Some May Be Serious’ category and the primary lay term, “Tiredness” is listed in the ‘Occasional, Some May Be Serious’ category, the symptom “Tiredness” should be removed from the “High blood pressure…” description, leaving “High blood pressure which may cause headaches or blurred vision”. This approach avoids duplication but allows patients to know that “tiredness” may occur with or without high blood pressure.
	2. Example: When “Infection” and “Infection, especially when white blood cell count is low” are both translated from two or more different scientific adverse events, “Infection” should be omitted and only “Infection, especially when white blood cell count is low” will be listed in the “possible side effects” table. If “Infection” is listed in the ‘Common, Some May Be Serious’ category and “Infection, especially when white blood cell count is low” is listed in the ‘Occasional, Some May Be Serious’ category, “Infection, especially when white blood cell count is low” should be listed in the ‘Common, Some May Be Serious’ category.
9. Scientific adverse events which are known only by abnormal laboratory results, with no accompanying symptoms should not be included in the risk lists as these will not be perceived by patients.
10. Guidelines for Internal bleeding, bleeding from multiple sites, vaginal bleeding, nose bleed, bleeding in testicles, bleeding in the brain, and blood in urine:
	1. When both the informed consent terms “Internal bleeding” and “Blood in urine” are translated from two different scientific adverse events:
		1. List Internal bleeding first.
		2. List all Symptoms associated with all internal bleeding, omitting duplicates.
			1. Example: “Internal bleeding which may cause black, tarry stool or coughing up blood”
		3. Then add “blood in urine” to the symptoms following “internal bleeding which may cause …”
			1. Example: “Internal bleeding which may cause black, tarry stool, coughing up blood, or blood in urine”
	2. When informed consent terms such as “Bleeding from multiple sites”, “bleeding in the testis”, “bleeding in the brain”, “vaginal bleeding”, and “nose bleeds”, are translated from multiple scientific adverse events, follow the guidelines below:
		1. List “Bleeding from multiple sites” first.
		2. “vaginal bleeding”, “nose bleed”, “bleeding in the brain”, and “bleeding in testis should be listed individually after “Bleeding from multiple sites”.
			1. Example: “Bleeding from multiple sites including the vagina, testis, or brain”
		3. List all associated Symptoms at the end.
			1. Example: “Bleeding from multiple sites including the brain which may cause headaches or confusion”
11. The *NCI Risk Term Library* provides guidance on informed consent terms that commonly occur together in a common body organ or system which can be listed on the same line.
	1. Example: If the informed consent terms “heart failure”, “heart stops beating”, and “heart attack” occur within the same frequency category, list them on the same line, followed by relevant symptoms.
	2. Example: If the informed consent terms, “nausea”, “vomiting”, and diarrhea” are translated from one or more scientific adverse events, they should be listed on the same line as, “Nausea, vomiting, diarrhea”.
	3. Example: “Abnormal menstrual period” and “abnormal sexual function” can be combined to say: “abnormal menstrual period, sexual function”.
12. The *NCI Risk Term Library* provides guidance on symptoms associated with similar informed consent terms that are translated from different scientific adverse events that may be combined on one line.
	1. Example: “Blood clots which may cause bleeding” and “blood clots which may cause belly pain” can be combined as “blood clots which may cause bleeding or belly pain”.
	2. Example: “Blurred vision” and “blurred vision which may cause blindness” can be combined as “blurred vision which may cause blindness”.
13. If the phrase “in children” or “in children or adolescents” is at the beginning of a term included in the risk list, the term only needs to be included if the study includes children or adolescents.
14. After the informed consent terms listed in the risk lists are sorted into the three tables by frequency of occurrence (i.e., Common, Occasional, Rare), the terms are then evaluated and curated. On a case-by-case basis, depending on the agent, symptom(s), adverse effect(s), and/or severity involved, adjustments or modifications may be made to listed term(s) and/or symptoms. Lastly, the remaining terms are ordered by relative risks within each frequency table by severity and affected organ or body system, according to general guidelines developed by NCI.†

## Procedure for developing or updating a regimen (combination of commercially available anticancer agents) risk list:

1. For anticancer regimens, risk lists are developed by aggregating the informed consent terms from two or more of NCI’s single agent risk lists.
2. Review each individual single agent risk list to determine if it needs to be created, reviewed, or updated prior to aggregating the terms for the regimen risk list.
3. Beginning with two single agents risk lists, the informed consent terms and associated symptoms are combined into one list. Duplicative terms and symptoms within the same frequency category are deleted. If duplicative informed consent terms and/or symptoms from each of the single agent lists occur with different frequencies (i.e., are listed in different frequency categories), the term should be removed from the less frequent category and placed in the more frequent category in the regimen risk list.
4. For regimens involving more than two agents, additional single agent risk list(s) can be combined with the developing regimen list one at a time until all adverse events for all agents included in the regimen are accounted for.
5. If the two single agent risk lists include duplicate terms – one as a primary informed consent term and the other as a symptom associated with another condition, the symptom should be omitted (unless the single agent “directions” indicate an exception) and the primary informed consent term should be listed, even if it is categorized as occurring less frequently.
6. Guidelines for combining informed consent terms as described in the previous procedures for developing single agent risk lists also apply to regimens (see #10, 11, and 12).
7. Reference documents related to risk lists for individual single agents included in the regimen may need to be consulted to recall the original scientific adverse event that an informed consent term is translated from in order to determine whether or not symptoms can be de-duplicated for some conditions.
8. After all informed consent terms have been aggregated for the regimen, terms should be categorized by frequency (i.e., Common, Occasional, Rare) and listed in a uniform manner within each frequency category, as done with single agent risk lists.† On a case-by-case basis, depending on the agents, symptoms, adverse effects, and/or severities involved, adjustments or modifications may be made to the grouping and listing of terms and/or symptoms on regimen risk lists.

## References:

* + - 1. Kupferberg N, Hartel LJ. Evaluation of five full-text drug databases by pharmacy students, faculty, and librarians: do the groups agree? J Med Libr Assoc. 2004;92(1):66-71.
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			5. Koyfman et al. A consent form template for phase 1 oncology trials. IRB. 2009 Jul-Aug;31(4):1-8.
			6. PRO-CTCAE language
			7. NCTN Group standard risk profiles for commercial agents.