Determining whether a study is considered a significant risk device study

Do you need an IDE?

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Significant Risk (SR)

- *Significant risk device* (812.3(m)) means an investigational device that:
  - 1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - **(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or**
  - (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- Example: Use of an investigational in vitro diagnostic test to select patients for a clinical trial.

Different types of devices

In Vitro diagnostic devices versus implanted devices

- Implanted device, i.e. prosthetic heart valve
- Risk of the trial is the same as the risk of the device

- In Vitro diagnostic device
- Risk of the trial depends on how the information generated by the device is used

Risk Determination for IVDs

- The clinical protocol gets the risk determination, not the device.
- The RD question for IVDs is:
- ***"What is the risk of the use of this device in this trial."***
- The use of the identical device can be either significant risk or non-significant risk depending on how it is used in the trial.

In vitro diagnostic devices

- Companion diagnostic devices for oncology trials
- Genomics devices- same general principles apply

Key questions with respect to risk:

Note: risk is conferred largely by the possibility of erroneous results

- Will the results from the device be used for enrollment?
- Will the results from the device cause patients to forego known effective/ approved therapy?
- Will the results from the device cause patients to be subjected to unacceptable toxicities?
- Will the results from the device cause patients to undergo a potentially high-risk biopsy?

Additional question

- Based on available data, is there a known biomarker effect with respect to either toxicity or effectiveness?

- Usually insufficient data.
- If there is a known effect, then use of the device could increase toxicity or divert patient from more effective therapy

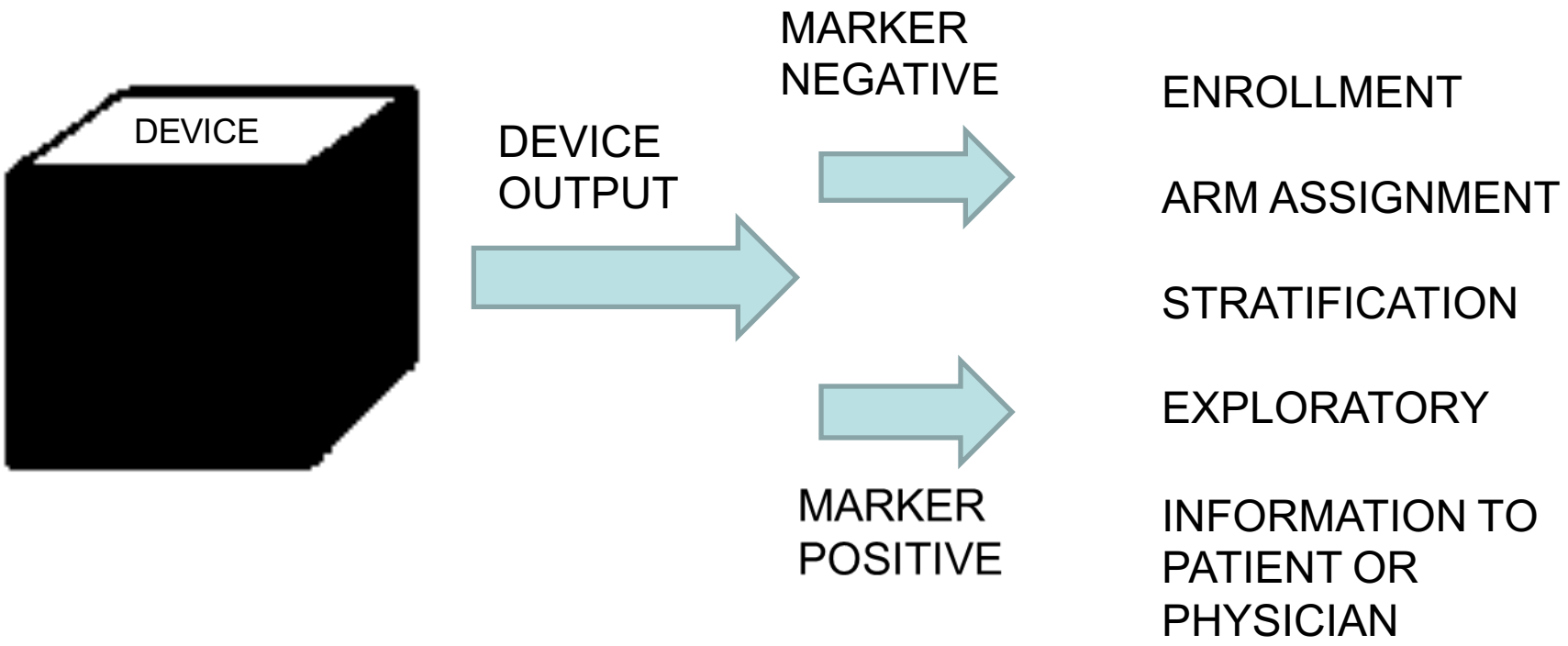
What is NOT considered in a risk determination

- Benefit or potential benefit
- Numbers of patients at risk
- Incorrect exclusion from a trial (as management is expected to revert to standard of care)

What's needed for a Risk Determination for IVD

- Complete clinical protocol for the trial
  - Inclusion/Exclusion criteria
  - Proposed interventions
  - How is IVD used to make decisions about treatment/enrollment.
- Device description
  - General understanding of the device
  - Sample requirements for device (i.e. Tissue, blood, buccal swab…)

Risk depends on the use of device output in trial



Enrollment

- If the device output is used as a criterion for enrollment, then the device exposes a patient to all the risks of being in the trial
- These risks could include foregoing known effective therapy, drug toxicities, new biopsies performed solely for trial purposes

Stratification

- A trial may be stratified using known or suspected prognostic indicators such as age, gender, smoking history

- If the device output is used for stratification within trial arms, then this does not change the risks to which the patient is exposed.
- However….

Stratification with possibility of affecting enrollment

- Example:
- Subjects will be accrued without respect to device results until 50 marker-negatives are enrolled. Subsequent to that point, only marker-positives will be enrolled.

- Result- same risk as marker-based enrollment

Arm assignment

- Patients will be enrolled regardless of device results.
- Arm A- marker positives
- Arm B- marker negatives

- This is generally considered NSR if there is equipoise; i.e. the arms are both of equal or unknown risks; however…

Arm assignment
Foregoing standard of care

- Arm A- Experimental agent
- Arm B- Standard of care treatment, known to be effective
- Arm A patients will forego known effective therapy, and accordingly an incorrect test result will potentially deprive a patient of alternative effective therapy. This is generally classified as an SR trial.

Arm assignment
Add-on to standard of care

- Arm A- Standard of care + experimental agent
- Arm B- Standard of care

- This setting would generally warrant an NSR determination because the investigational agent is an “add-on” to standard of care (absent excess toxicity associated with the investigational agent)

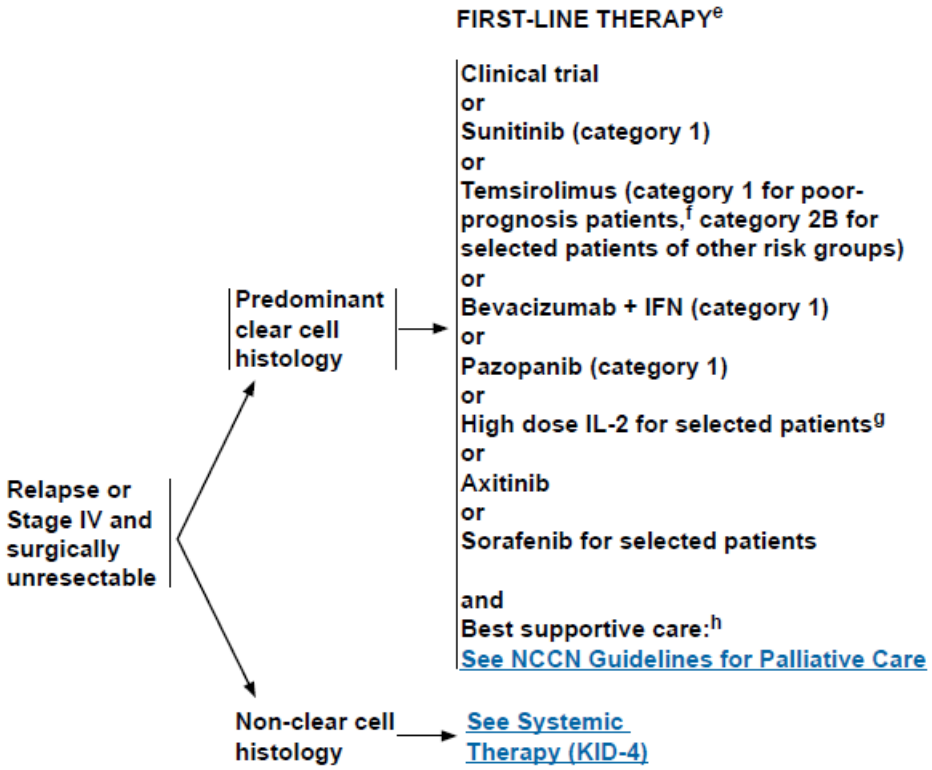
Arm assignment
Severe toxicity

- Arm A- Standard of care + experimental agent with expected severe toxicity
- Arm B- Standard of care

- This setting would generally warrant an SR determination because of added toxicity beyond that expected with standard of care agents, notwithstanding the fact that it is an "add-on" to standard of care.

Standard of care

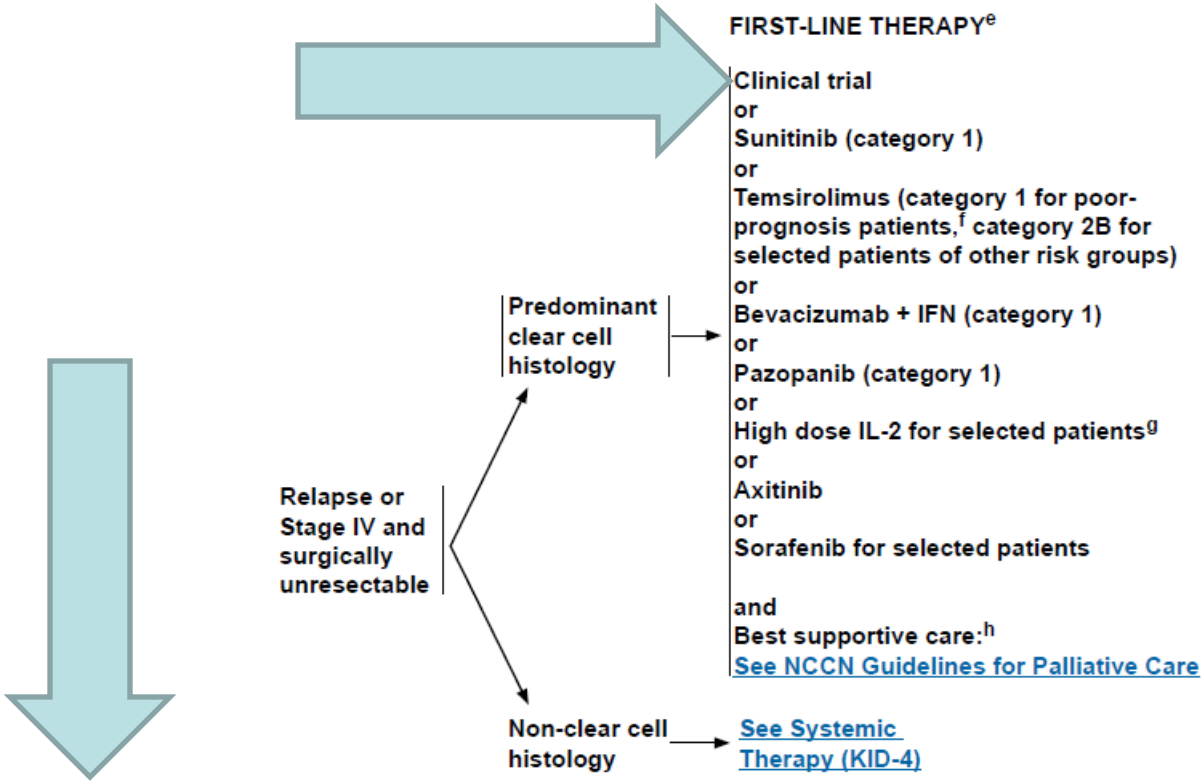
NCCN Guidelines



Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines

(renal cell carcinoma)



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Biopsy risk

- If enrolled patients will undergo a biopsy beyond what would be considered standard of care for the sole purpose of development of the test/device, then the risks of the biopsy are attributed to the device.
- Accordingly, a high risk biopsy in this setting would generally warrant an SR determination

Biopsy considerations

- Biopsy risk depends on:
  - Site of procedure
  - Type of procedure
  - Patient's disease and underlying health
  - Institutional experience and support capabilities
- In the context of the trial, biopsy risk is controlled according to the clinical judgment of the health care providers

Biopsy considerations

Examples of potentially high-risk biopsies:

lung, mediastinum, brain, pancreas

Examples of biopsies that are likely low-risk:

skin, endoscopic GI, cervix

Biopsy considerations

- It is acknowledged that, in studies of recurrent/end-stage cancer, the site that will need to be biopsied may not be known in advance (when the protocol is written)
- A patient on a clinical trial using an investigational device should not undergo a high-risk biopsy **solely for device development** unless there is an approved IDE

Summary

- It is not the device itself that is “high risk” or “low risk”
- Risk determination depends on the specific use of the device in a specific trial
- Risk depends on how the output of the device is used in the clinical trial under consideration