Terminology in a clinical trial

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Clinical trials definition

Clinicaltrials.gov definition

"A clinical trial is a research study to answer specific questions about

- vaccines *or*
- new therapies *or*
- new ways of using known treatments"

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Type of clinical trials

Types and goals in 2000

	Phase I	Phase II	Phase III
Goal	MTD	Activity	Comparison SOC
Objective	Safety	Activity	Efficacy
Endpoint	DLT	Response	Survival
N sample	20-60	20-200	200-2000
Registration	No	Limited	Powerful

Type of clinical trials

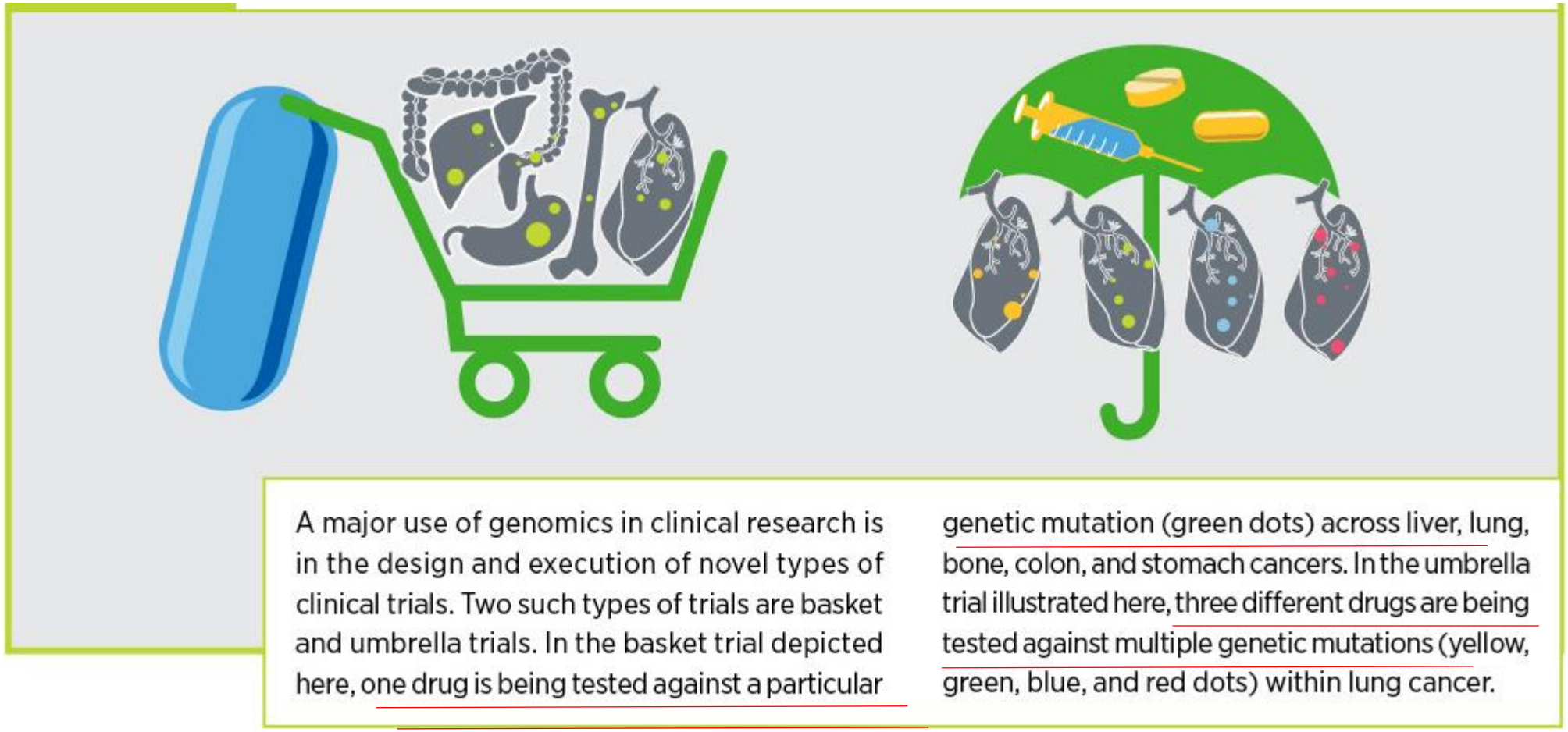
Types and goals in 2019

	Phase I/Phase II	Phase III
Goal	MTD/Activity	Comparison SOC
Objective	Safety/Activity	Efficacy
Endpoint	DLT/Response	Survival
N sample	100-1000	200-2000
Registration	Real	Powerful

Type of clinical trials

BASKET

UMBRELLA

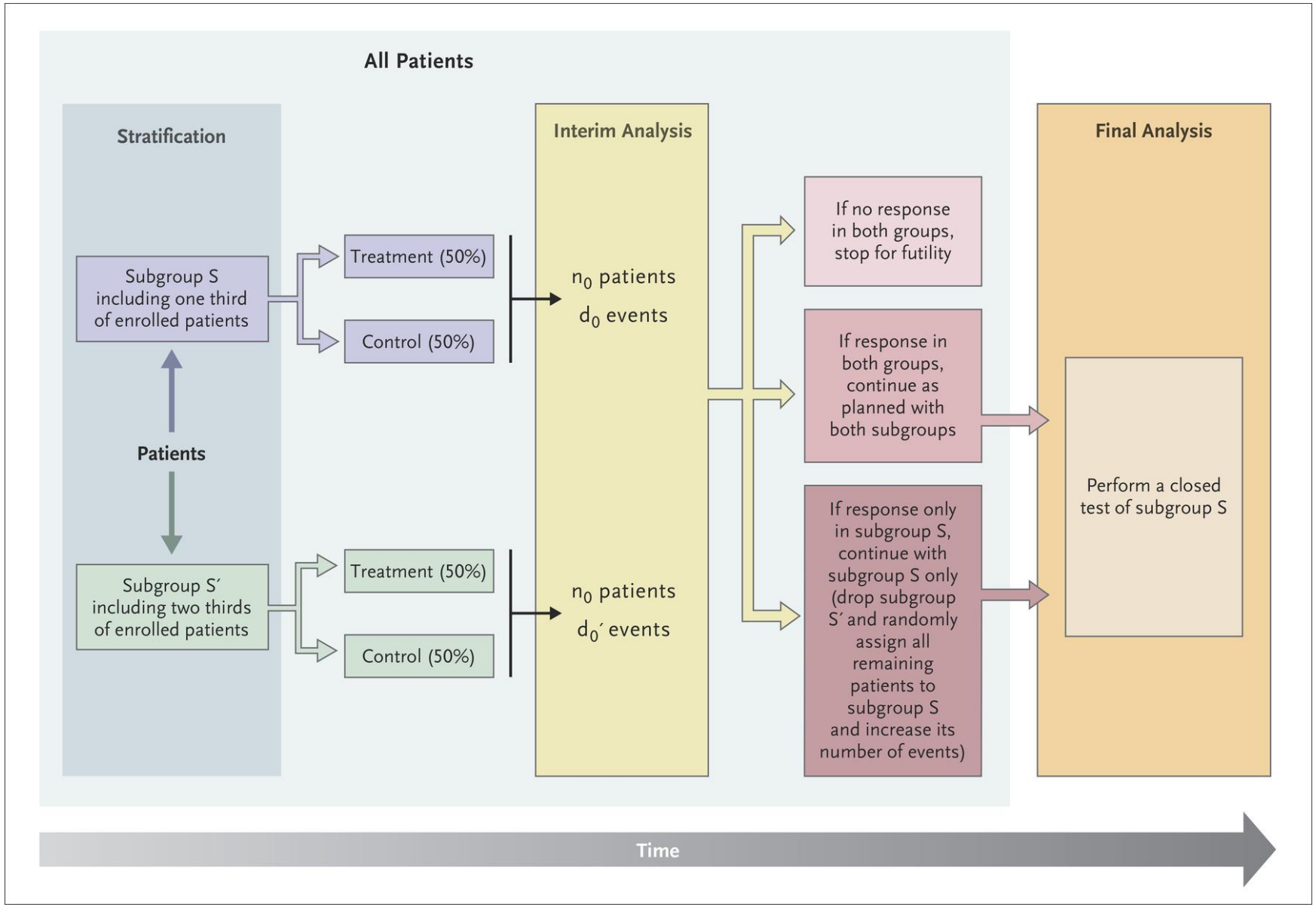


A major use of genomics in clinical research is in the design and execution of novel types of clinical trials. Two such types of trials are basket and umbrella trials. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, bone, colon, and stomach cancers. In the umbrella trial illustrated here, three different drugs are being tested against multiple genetic mutations (yellow, green, blue, and red dots) within lung cancer.

American Association for Cancer Research (AACR) Cancer Progress Report 2017

Type of clinical trials

Adaptive trials



Bhatt, Nejm, 2016

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OBJECTIVES

- Outlines the research question related to the aim of the study
- Concrete
- Clearly specified
- Examples: Toxicity

  Response

  Survival

OBJECTIVES

Primary objective

- Main objective
- Statistical design depends on it

  Sample size

  Power

  Alpha error

- There might be 2 primary objetives, but…

  remember to split alpha risk

Secondary objective

- Important
- Do not affect design but
- Designs affects it (sample size, power…)

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ENDPOINTS

Quantitative measurement or data point needed to meet the objectives

Types:

- Binary
- Ordinal
- Continous
- Event time
- Categorical

Type	Example	Example value
Binary	Post op complications	Yes-No
Ordinal	Tumor response	CR, PR, SD, PD
Continous	QOL score	0-100
Event time	Time to death	Months from treatment start to death
Categorical	Toxicities	Common toxicities (no grade)

ENDPOINTS

Clinical endpoint

Represent direct benefit

survival

decrease pain

abscense of disease

Surrogate endpoint

Do not represent direct benefit

Correlates with clinical benefit

Features

- Valid
- Highly correlated with outcome
- Yield same statistical inference as the definitive endpoint

Tumor response –OS

PFS—OS

pCR—OS

ENDPOINTS

Definition	Example 1	Example 2
Objective	To compare efficacy (ORR) of drug A vs drug B	To compare efficacy (OS) of drug A vs drug B
Endpoint	Best overall reponse defined by CR, PR, SD or PD by RECIST 1.1	Survival time for each patient, defined as the difference in time from the start of treatment to death or last contact
Statistic	Response frequency defined as the proportion of all treated patients who have complete or partial response	Overall survival distributions estimated using Kaplan–Meier method, and median survival time for each treatment group; hazard ratio estimated as a summary of treatment effect on risk of death

ENDPOINTS

Patient centered endpoints

1. **OS**: **the time from randomization or start of treatment** to *death* due to **any cause**, including death from the trial disease or unrelated conditions.

   Affected by other treatments beyond the trial

   Affected by adverse events

   BE CAREFUL

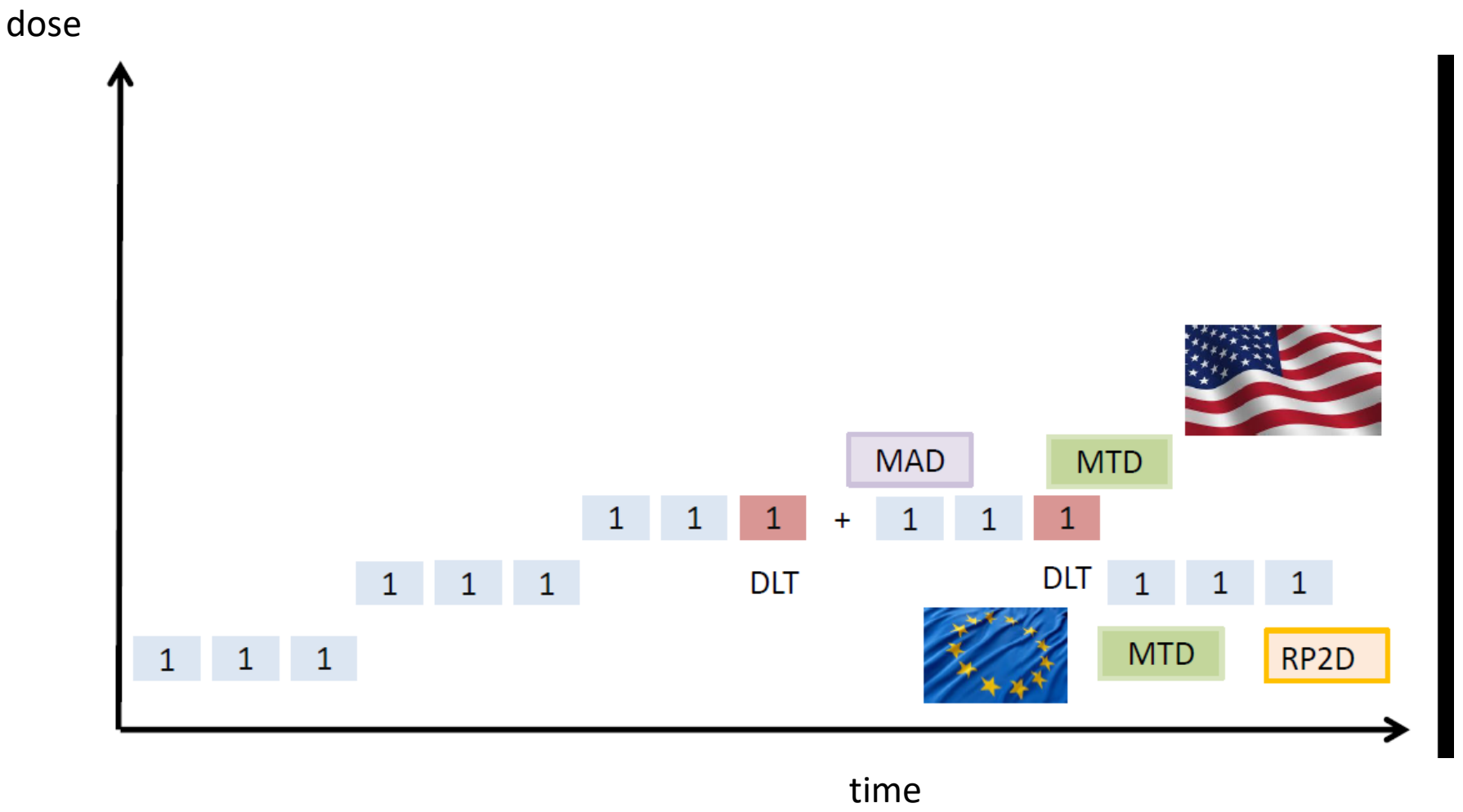
   Censored survival time: the time from the start of treatment to the date of last contact with patients who are alive.

   Competing risks: if follow up time is very long patients may die from other causes

2. **Toxicity**

   DLT: Dose limiting toxicity

ENDPOINTS



ENDPOINTS

Patient centered endpoints

3. Health related quality of life

HRQOL is the effect of cancer and treatment on the well-being of an individual patient

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling t number that best applies to you. There are no "right" or "wrong" answers. The information that you provide w remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good

ENDPOINTS

Tumor centered endpoints

1. **PFS**: **the time from start of treatment or randomization until disease progression or death.**
   Not affected by treatment beyond the trial
   Sometimes it is a surrogate for OS

   BE CAREFUL
   Timing for tumor analysis
   Real time of progression: unknown, but it is a valid surrogate (interval censored data)

2. **Time to progression: the time from start of treatment or randomization until disease progression**
   Deaths are not considered as event
   Deaths are censored

3. DFS: is defined as the duration between treatment start and relapse of disease or death from any cause.
   After surgery
   May be a good surrogate (long follow up)

Tumor centered endpoints

4. Objective response rate

Proportion of patients who have tumor size reduction of a predefined amount for a minimum time period

CR + PR

5. Disease control rate

Proportion of patients who have tumor size reduction or stable disease of a predefined amount for a minimum time period

CR + PR + SD

6. Duration of response

Time from initial tumor response (complete or partial response) to tumor progression and often is reported with objective response rate.

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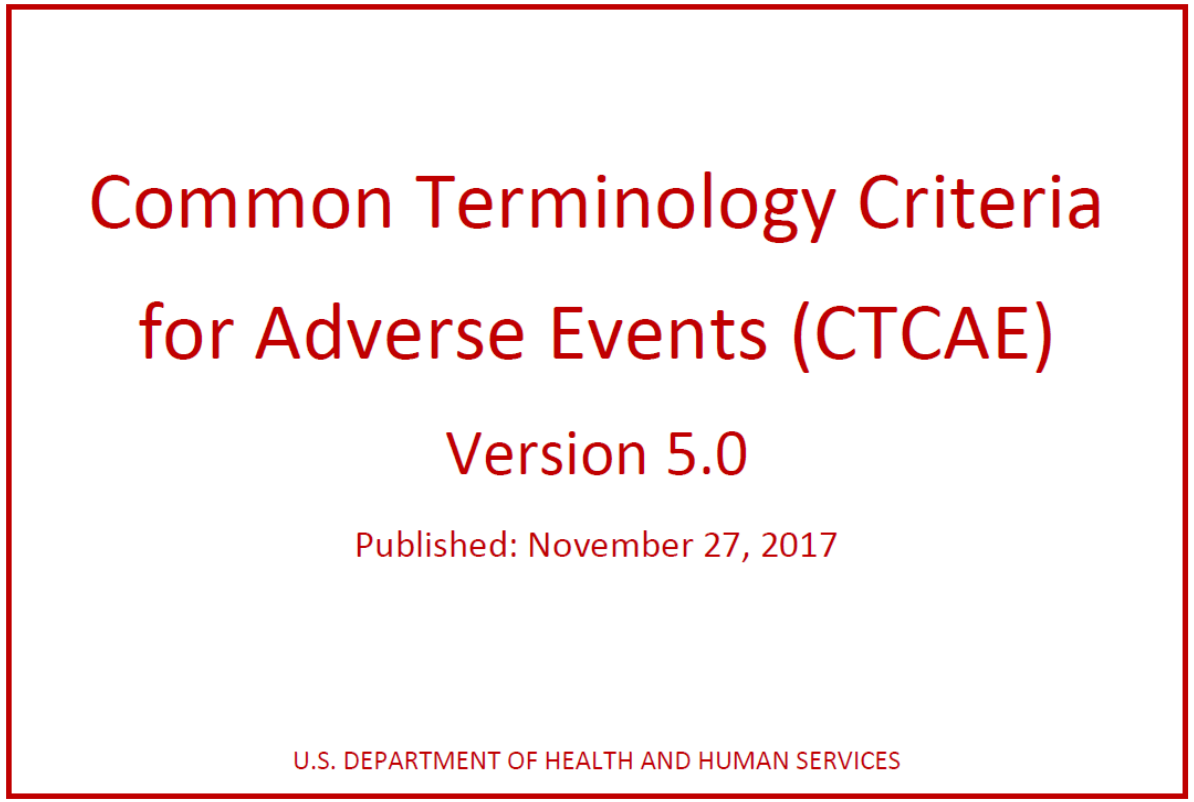
Adverse event:

Any **unfavorable** and **unintended sign** (such as laboratory finding), symptom, or disease that occurs while a patient is enrolled in a clinical trial.

Maybe **related or not** to IP

Maybe **relevant or not** regardless of relation to IP

Grading CTCAE



Serious adverse event: (FDA definition)

Any AE that results in:

- death,
- illness requiring hospitalization,
- events deemed life-threatening,
- persistent or significant disability/incapacity,
- a congenital anomaly/birth defect,
- or a medically important condition

Adverse events of Special Interest

An adverse event of special interest (serious or non-serious) is:

An event of scientific and medical concern specific to the **sponsor's** product or program

Requires:

ongoing monitoring
rapid communication by the investigator to the sponsor.

Such an event might warrant further investigation in order to characterize and understand it

MUST BE REPORTED in < 24 hours since it has been noticed

	Truth	
Hypothesis	No effect	Effect
No effect	Correct	Error type II
Effect	Error type I	Correct

Error alpha = Saying that a drug is useful when it is NOT

Erro beta = Saying that a drug is NOT useful when it REALLY is

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