ENGAGe - ENGOT
Clinical Trials Project

STUDY BOOK
for the participants of the Clinical Trials Project

ENGAGe
ESGO | European Network of Gynaecological Cancer Advocacy Groups

ENGOT
European Network of Gynaecological Oncological Trial groups

ESGO
European Society of Gynaecological Oncology

Introduction

ENGAGe has started a new project where we will try to get 'patient experts' involved in the design and implementation of clinical trials so that the patient perspective may be taken into account in all aspects of the study.

ENGAGe is working with ENGOT on this project, and the first 3 webinars were held on Sept. 2, 2019.

The participants in the project have also had access to all presentations during SoA – a virtual conference organised by ESGO and held from 14 to 16 December 2020.

There will furthermore be 5 webinars for this patient group in the spring of 2021.

The objective is to educate a number patients from major European countries to a level where they will be able to understand the process of a clinical trial and contribute with useful insight from a patient perspective.

The webinars from September 2, 2019 covered the topics:

- Terminology in a clinical trial
- Study methodology – single arm, dual arm, prospective, retrospective
- Informed consent, PRO (Patient Reported Outcome), side effects etc.

You can view the webinars at https://engage.esgo.org/for-members/ct-project-participant/

The intent of this study guide, which consists of a report of the webinars and a summary with comprehension questions, is to make it easier for the viewer to grasp the concepts presented in the webinars from September 2, 2019.

The webinar is a joint project between two ESGO networks, ENGAGe and ENGOT.

ENGAGe is the European Network of Gynaecological Cancer Advocacy Groups.
Learn more at **engage.esgo.org**

ENGOT is the European Network of Gynaecological Oncological Trial groups.
Learn more at **engot.esgo.org**

Featured speakers:

Dr. Murat Gultekin, ENGAGe Co-chair
Dr. Eduardo Castañón Álvarez, Medical Oncology, CUN, ES
Dr. Mansoor Raza Mirza, Chief Oncologist, Rigshospitalet, DK
Dr. Kristina Lindemann, Consultant, Oslo University Hospital, NO

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Report of the webinars

by Birthe Lemley

Terminology in a clinical trial presented by Dr. Eduardo Castañón Álvarez

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Definition of a clinical trial

Trials to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on large groups of people.

For some patients, clinical research trials represent an avenue for receiving promising new therapies that would not otherwise be available. Patients with difficult to treat or currently „incurable" diseases, such as certain types of cancer, may want to pursue participation in clinical research trials if standard therapies are not effective. Clinical research trials are sometimes lifesaving.

■ There are four possible outcomes from a clinical trial:

Positive trial -- The clinical trial shows that the new treatment has a large beneficial effect and is superior to standard treatment.

Non-inferior trial -- The clinical trial shows that that the new treatment is equivalent to standard treatment. Also called a non-inferiority trial.

Inconclusive trial -- The clinical trial shows that the new treatment is neither clearly superior nor clearly inferior to standard treatment.

Negative trial -- The clinical trial shows that a new treatment is inferior to standard treatment.

Source: https://www.medicinenet.com

You can find all clinical trials at clinicaltrials.gov

Types of clinical trials

Phase I—focuses on the maximum tolerated dose (MTD) and the safety of the drug. The endpoint is DLT dose limiting toxicity (DLT). Small number of patients involved (20-60). Phase I is sometimes combined with the Phase II study.

Phase II—focuses on efficacy of the drug against the cancer (response); medium number of patients involved (20-200). In rather rare cases a drug gets approval after a phase II study.

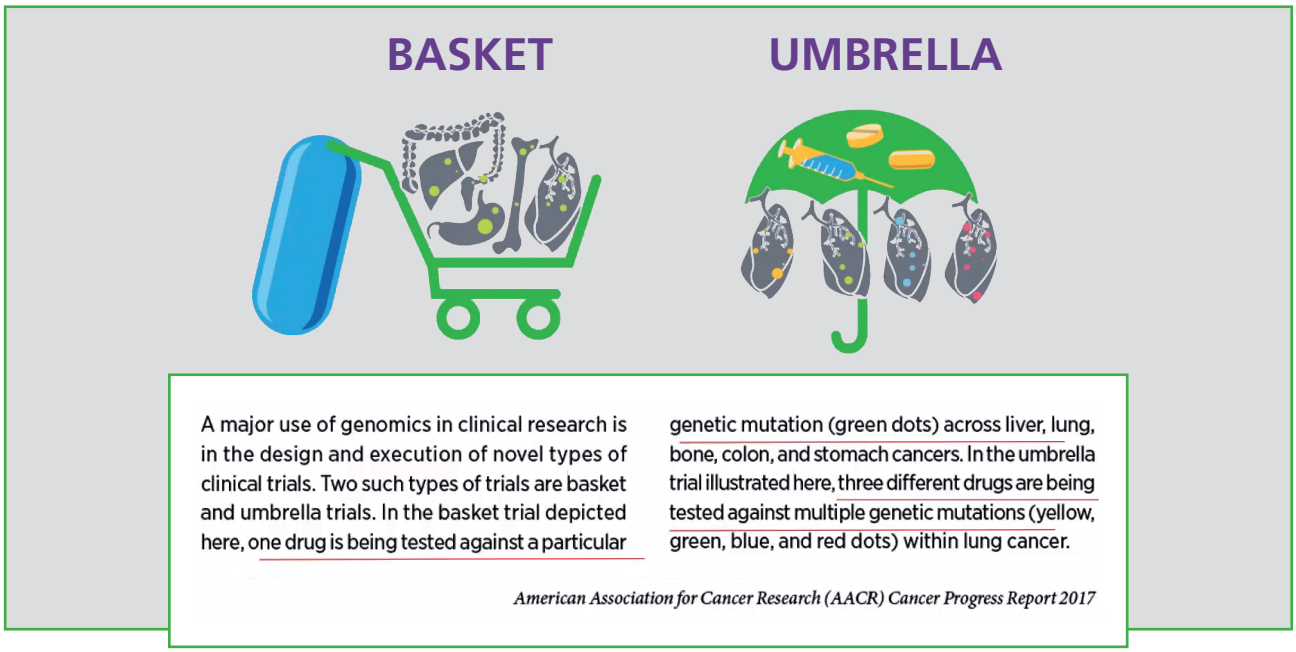
Phase III—focuses on comparing the standard of care (SOC) against what is being studied; tries to determine efficacy of the drug; focuses on survival and involves large number of patient (200-2000). It is the most powerful study for being able to register a new drug for approval e.g., by the FDA (US Food and Drug Administration or EMA (European Medicines Agency).

Basket and umbrella trials

Both types of trials are based on genomics in clinical research.

In a basket trial one drug is being tested against a particular genetic mutation across liver, lung, bone, colon, and stomach cancers.

In an umbrella trial different drugs can be tested against multiple genetic mutations in a specific type of cancer.



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

Adaptive trial

A trial in which the parameters of the trial are adjusted (adapted) as the investigators record their observations; can incorporate different patient types and different tumour types.

Types of errors—may be due to trial design; (probability calculated as a percentage)

Alpha error/Type I error—when a trial deems a drug or therapy not effective but in fact it is

Beta error/Type II error—when a trial deems a drug or therapy effective, but it is not

Objectives

Outlines the research questions related to the aim of the study. They must be concrete and clearly specified. **The research questions could be on:**

- ✔ **Toxicity**
- ✔ **Response to treatment**
- ✔ **Survival** – could be overall survival or progression-free survival according to the disease.

Objectives are usually split into:

Primary objective

The primary objective of the trial is to address the scientific question by collecting appropriate data. The primary objective could be: To compare efficacy on objective response rate (ORR) of drug A versus drug B, or to compare efficacy on overal survival (OS) of drug A vs drug B.

The statistical design depends on the main objective of the trial (sample size, power, alpha error).

There can be 2 primary objectives.

Secondary objective

Important

Does not affect design, but the design might affect the secondary objective (sample size etc.)

Endpoints

Quantitative measurement or data point needed to meet the objectives

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)

Acronyms and abbreviations:

Post op = Post (after) operation
CR = Complete Response
PR = Partial Response
SD = Stable disease
PD = Progressive disease
QoL = Quality of life

Clinical endpoints:

Represent direct benefits, such as survival, decrease of pain, absence of disease

Surrogate endpoints:

Tumor response

OS = overall survival
PFS = Progression-free survival
pCR = pathologic complete response

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 response 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

Explanations of terms

RECIST 1.1: Response evaluation criteria in solid tumors

(Response Evaluation Criteria in Solid Tumours) provides a simple and pragmatic methodology to evaluate the activity and efficacy of new cancer therapeutics in solid tumors, using validated and consistent criteria to assess changes in tumor burden. Source: https://recist.eortc.org/

The Kaplan-Meier method

The Kaplan–Meier estimator, also known as the product limit estimator, is a non-parametric statistic used to estimate the survival function from lifetime data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment. Source: Wikipedia

Hazard ratio

A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups. Source: National Cancer Institute

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

Patient-centered endpoints can also be HRQOL (Health-related quality of life).

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

Below is an example of a questionnaire on HRQOL:

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					
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

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
	Regardless of you current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this ☐ box and go to the next section.					
GS7	I am satisfied with my sex life	0	1	2	3	4

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 of 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)

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.

Acronyms:

Objective response rate = ORR
Disease control rate = DCR
Duration of response = DOR
Disease-free survival = DFS

Adverse events/ serious adverse events/ adverse events of special interest

Adverse events (AEs)

Any unexpected medical problem that occurs while a patient is enrolled in a clinical trial.

Adverse events may be mild, moderate, or severe, and may be caused by something other than the drug or therapy given.

Serious adverse events (SAEs)

A Serious Adverse Event is any untoward medical occurrence or effect at any dose, any undesirable or unintentional effect that:

- ✔ results in death (regardless of cause)
- ✔ is life-threatening
  - places the subject, in the view of the investigator, at immediate risk of death at the time of event
  - It does not refer to an event, which hypothetically might have caused death if it were more severe.
- ✔ results in subject hospitalization (overnight stay) or prolongation of existing in subjects' hospitalization, unless hospitalization is for:
  - hospitalization that does not necessitate an overnight stay.
  - routine scheduled treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - planned prior to subject entering in the trial
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication treated in the trial and which has not worsened since the start of treatment with the investigational medicinal product
- ✔ results in persistent or significant disability or incapacity of the subject
  - disability is a substantial disruption of a person's ability to conduct normal life functions
- ✔ is qualified as "other" important medically significant event or condition e.g., the event may jeopardize the subject or may require intervention to prevent one of the outcomes listed above (e.g., intensive treatment in an emergency room or at home).

Adverse Event of Special Interest (AESI)

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, which requires

✔ Ongoing monitoring

✔ Rapid communication by the investigator to the sponsor.

MUST BE REPORTED in less than 24 hours after it has ben noticed.

Question on Alpha Error

After the first presentation there was a question as to the meaning of Alpha Error.

✔ **Alpha error** - drug is not effective, but this could be because the trial has not been designed properly. If the P-value is greater than 0.05, it is less likely that the drug is effective, example Study 19 with olaparib for BRCA-mutated patients with ovarian cancer. The alpha error was 0.2 which means that there was a 20% risk that the drug was not effective. However, the investigator could still prove that it was effective although there was a high alpha error.

✔ **P Value:** $P > 0.05$ is the probability that the null hypothesis is true. A statistically significant test result ($P \leq 0.05$) means that the test hypothesis is false or should be rejected. A P-value > 0.05 means that no effect was observed.

✔ **Beta error:** The statistical error (said to be 'of the second kind,' or type II) that is made in testing when it is concluded that something is negative when it really is positive. Also known as false negative.

Source: https://www.medicinenet.com/

Methodology

Study methodology – single arm, dual arm, prospective, retrospective by

Chief Oncologist Mansoor Raza Mirza,

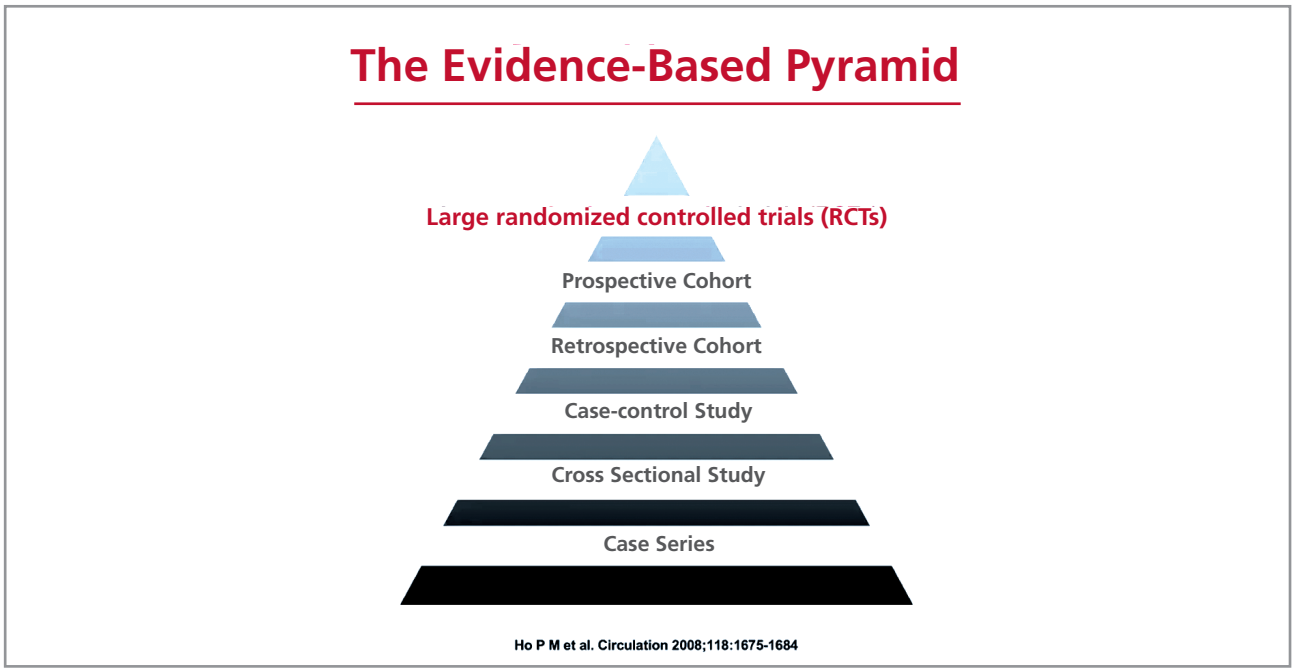
Why do we need clinical trials?

We need best evidence, i.e., level one evidence, before any treatment becomes available as Standard of Care to the patient.

How do we know that carboplatin and paclitaxel are effective in ovarian cancer? It has been proven through a clinical trial.

Previously we could try the drug on cell lines, then on animals, but that is not always the case anymore. It is not possible in Immunotherapy.

Large randomized controlled trials



On the highest step in the pyramid are the randomized trials where patients in the one arm get the new drug and patients in the other arm get placebo/standard of care. (Cancer patients only get placebo if there is no other treatment e.g., between relapses of the disease). Recently, it has been the custom to divide the arms so that 2/3 of the patients get the new drug and 1/3 get placebo/standard of care. Sometimes there is a chance of cross-over. This means that if the new drug is very effective, the patients in the placebo arm has a possibility of crossing-over to the arm with the new drug. This is beneficial for the patients, but a drawback for the investigator/the company or institutions behind the trial, as it can become more difficult for them to prove the efficacy of the drug as the comparison with the placebo/standard of care arm gets blurred.

Before a trial is started, there is an idea – a so-called hypotheses that the new drug will work better than placebo/standard of care.

A Prospective Cohort Study

A research study that follows groups of individuals over time, who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke and those who do not smoke) and compares them for a particular outcome (such as lung cancer). A prospective study is a forward-looking study.

A Retrospective Cohort Study

A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is already established at the start of the study. In other words, it is a study in which the data of patients are analysed when they have already achieved an outcome.

A Case-control Study

A case–control study (also known as case–referent study) is a type of observational study in which two existing groups differing in outcome are identified and compared on the basis of some supposed causal attribute. Case–control studies are often used to identify factors that may contribute to a medical condition by comparing subjects who have that condition/disease (the „cases") with patients who do not have the condition/disease but are otherwise similar (the „controls")

A Cross-sectional Study

A cross-sectional study is defined as a type of observational research that analyzes data of variables collected at one given point in time across a sample population or a pre-defined subset. This study type is also known as cross-sectional analysis, transverse study, or prevalence study.

Case Series

Observations made on a series of individuals, usually all receiving the same intervention, before and after an intervention but with no control group.

The lowest evidence in the pyramid is the case series.

It is not enough that your doctor says the drug will be effective. The level of evidence increases as we go up the pyramid until we come to the Randomised Controlled Trials (RCTs). These are comparative trials comparing standard of care against a new drug. The trials are randomized. This means that the patients are randomly assigned, which is usually done by computer, to receive either standard of care or the new treatment. The trial is usually blinded, meaning that the patient does not know whether he/she gets the new drug or placebo/standard of care. If the trial is double-blinded, then neither the patient nor the doctor knows which treatment the patient is getting. This is to avoid bias. Randomisation can be done with drugs and injections, but of course not if surgery is involved.

Two examples of poorly designed trials were mentioned during the webinar.

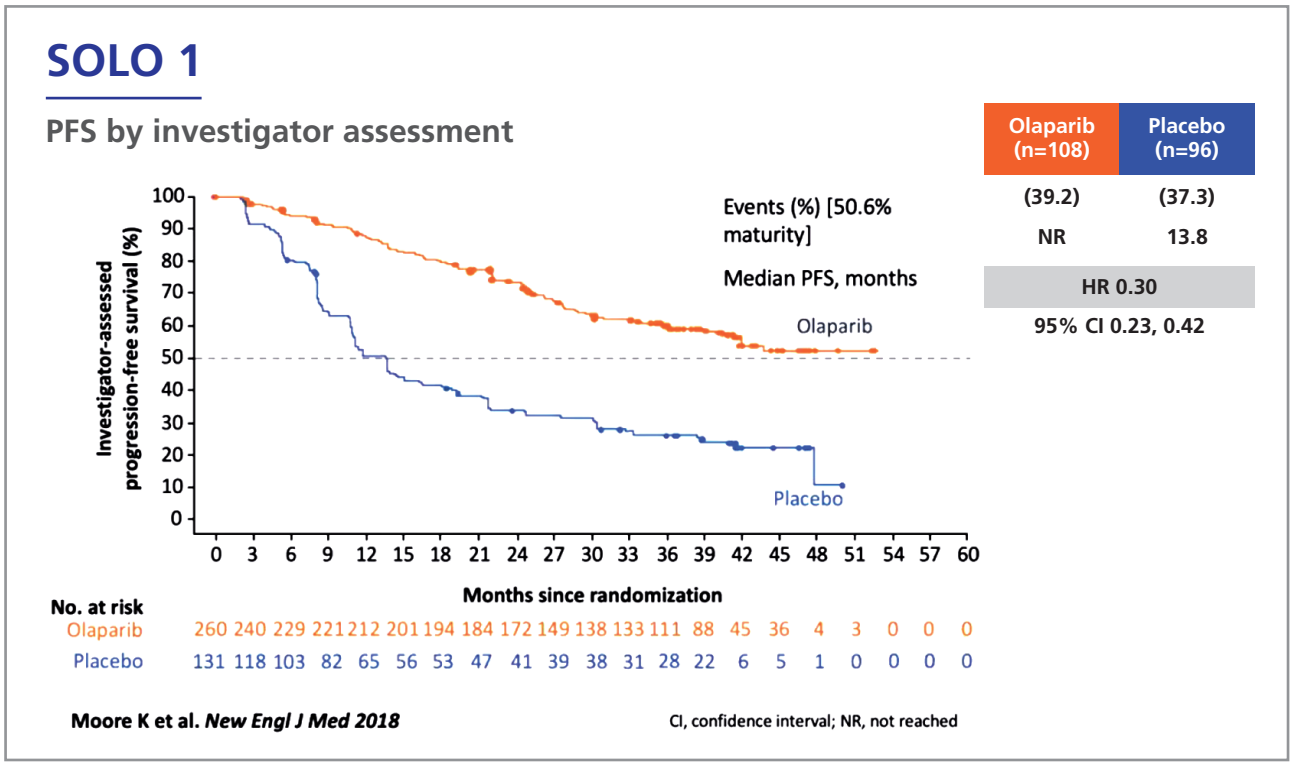
One was ovarian cancer in phase II. The trial was not randomized. An extra chemotherapy was just added on top of the two treatments that were standard of care:

Standard of care was carboplatin + paclitaxel. The drug gemcitabine was added, and there was response in all patients. Should we then all be happy? If we don't randomize, then we don't know if this is actually a better treatment than standard of care. In this case it wasn't. The patients did just as well on standard of care with the two drugs carboplatin + paclitaxel. There was only one difference. Worse toxicity for the patients from the third drug added to the other two.

Another trial was mentioned – i.e., the Javelin Ovarian 200 trial for patients with platinum-resistant disease. Patients were on weekly paclitaxel and avelumab was added. However, immunotherapy (in this case avelumab) does not work in all patients. We have to have biomarkers to find out what is working and what is not working on the patient.

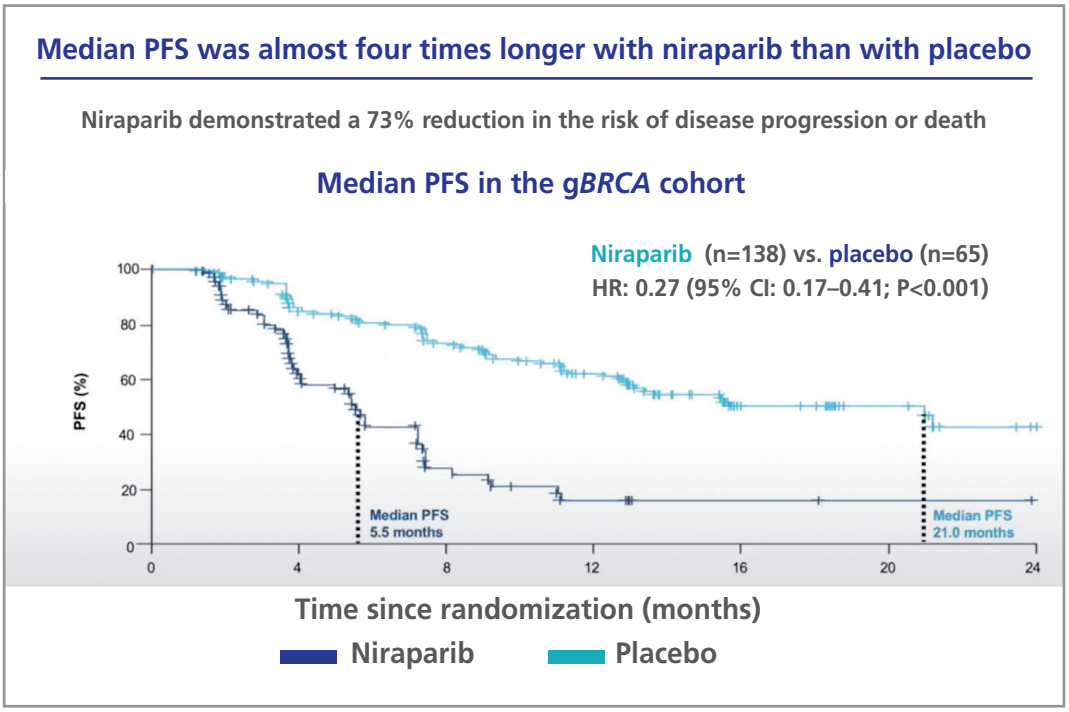
We need molecular profiling to find drugs for the patients that give max. efficacy for all.

Clinical trial SOLO1 for patients with high-grade serous ovarian cancer as maintenance in first-line treatment.



The PARP-inhibitor olaparib was given as maintenance treatment to patients with ovarian cancer and a BRCA-mutation, and by investigator assessment there was a very high chance of efficacy. This proved to be correct. Therefore, it is important to find the biomarker and then do the trial.

Clinical trial NOVA for patients with relapse of high-grade serous ovarian cancer as maintenance treatment.



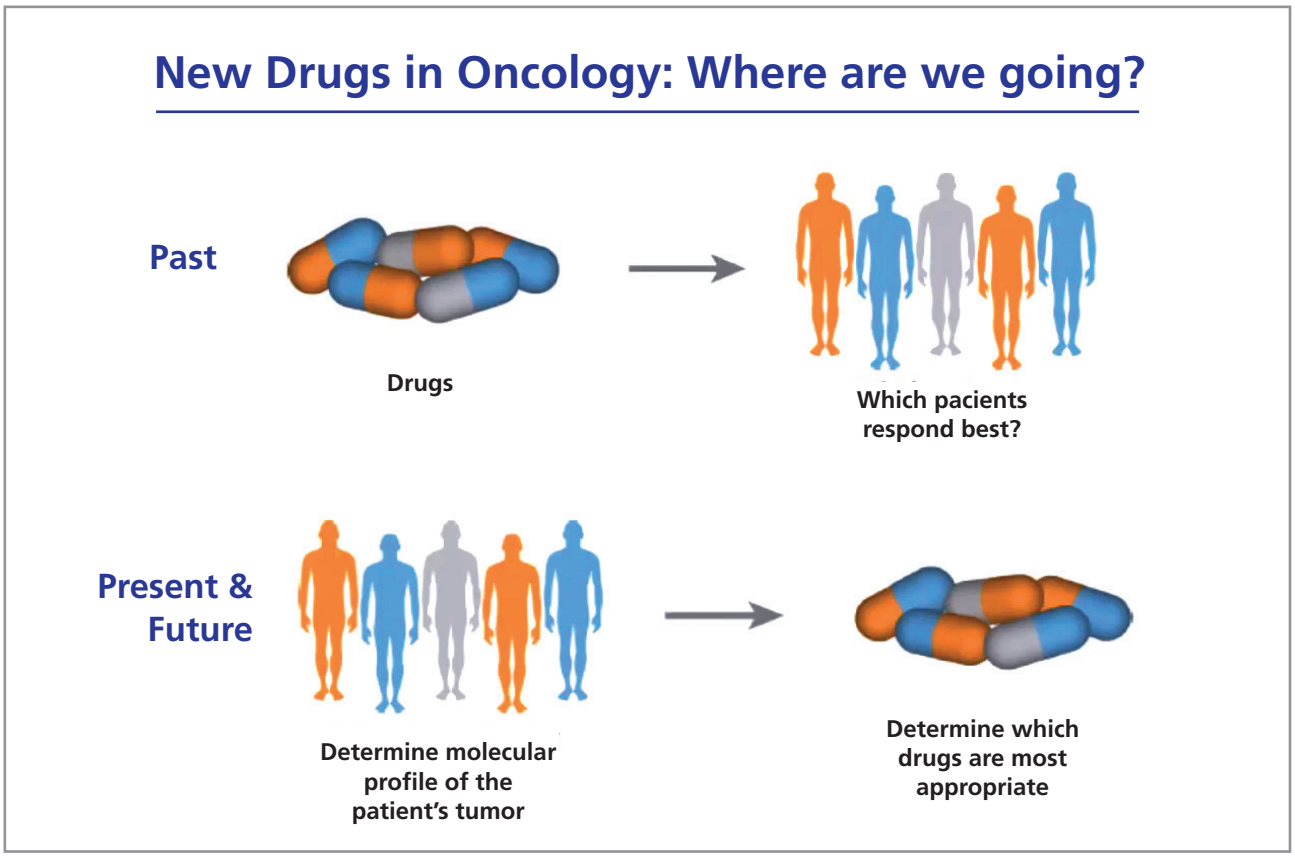
The above slide is from the NOVA study with the PARP-inhibitor niraparib for maintenance therapy of ovarian cancer patients in relapse. It shows the efficacy of the treatment for BRCA-mutated patients.

Median PFS for patients on placebo (no treatment which is standard of care) was **5,5 months**

Median PFS for patients on niraparib was **21,0 months**

In other words, we need to find the predicative biomarker to render max. efficacy of the drug.

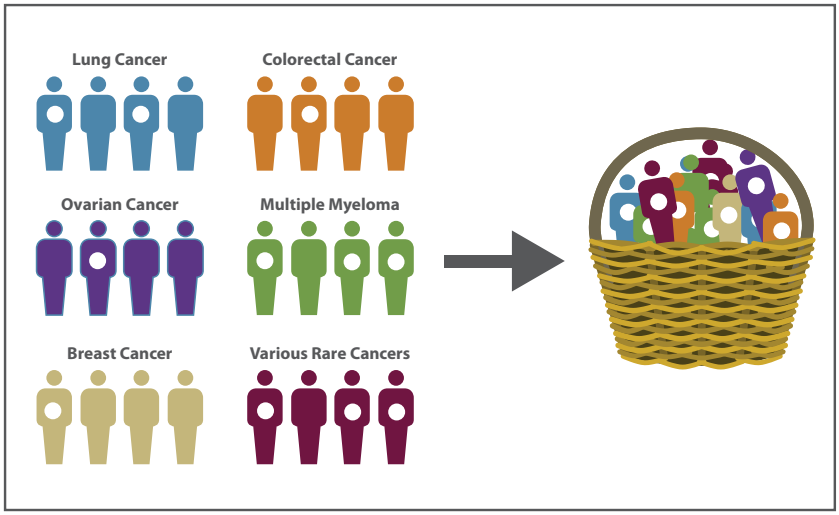
In order to achieve that, we need translational research to find the right biomarker and then the right treatment for the right patient. We need to divide patients into different subgroups. There are so many different mutations in the various gynaecological cancers.



Determining the molecular profile of the patient's tumor

Other types of trials(RTCs)

Basket trial (also mentioned on page 3)



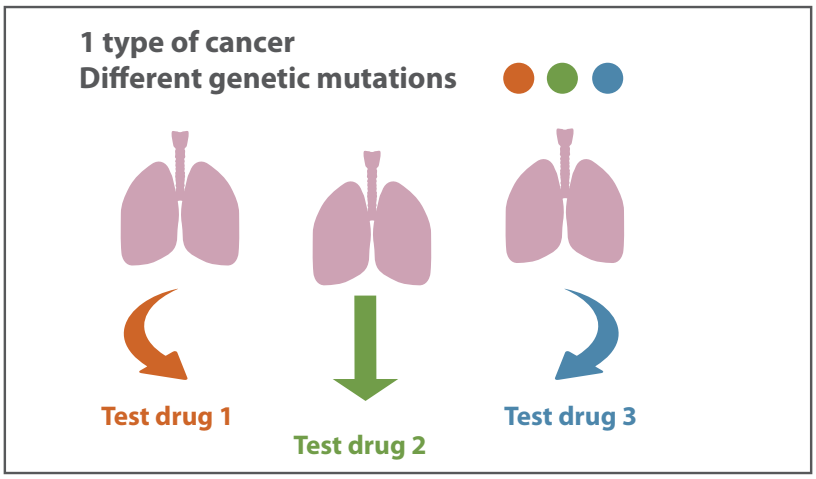
Definition from NCI Dictionary of cancer terms: A type of clinical **trial** that tests how well a new drug or other substance works in patients who have different types of cancer that all have the same mutation or biomarker. In **basket trials**, patients all receive the same treatment that targets the specific mutation or biomarker found in their cancer.

Several cancer types with focus on a specific genomic aberration – screen patients and create study.

Umbrella trial

(also mentioned on page 3)

One cancer trial – several drugs, several mutations, also sometimes combination of drugs. These types of studies are difficult to carry out for the pharmaceutical companies as they involve drugs from different companies.



Definition from NCI Dictionary of cancer terms: A type of clinical trial that tests how well new drugs or other substances work in patients who have the same type of cancer but different gene mutations (changes) or biomarkers. In umbrella trials, patients receive treatment based on the specific mutation or biomarker found in their cancer. The drugs being tested may change during the trial, as new targets and drugs are found. Umbrella trials may allow new drugs to be tested and approved more quickly than traditional clinical trials.

Evidence-based drugs

Mainstream should be to offer evidence-based drugs based on the patient's molecular profile, and then ask the patient to enter the trial.

It is not enough to have read in a paper that a drug is efficient. We need evidence – also in surgery.

Informed consent, PRO (Patient Reported Outcome), side effects etc.

Kristina Lindemann, Consultant

Informed consent

Nothing was written down about patients' rights until The Nuremberger Code in 1947 stating that "The voluntary consent of the human being is absolute essential."

This was first publicly mentioned in 1957 when there was a case in the US with a patient, who was paralyzed after a procedure with imaging. He claimed that he had not been properly informed and sued the doctors for malpractice. Many lawsuits from other patients followed, mainly in the US.

In 1966 the American anesthesiologist Henry Beecher talked about the adherence to ethical standards. He was also fighting for placebo being used in clinical controlled trials.

Today the informed consent process is regulated under Good Clinical Practice in Medical Research (The Declaration of Helsinki - first adopted in 1964).

In the case Canterbury vs Spencer in 1972, the patient was operated for a herniated disc and was paralyzed after the operation. The patient claimed that he had not been properly informed of the surgery and procedure prior to the operation and sued the doctor for malpractice.

Therefore, if surgery is required, the surgent should discuss the diagnosis, the surgical procedure, and the risks with the patient. The patient must also be made aware of alternative treatments.

The expected results of a clinical trial and of the alternative standard of care should also be discussed.

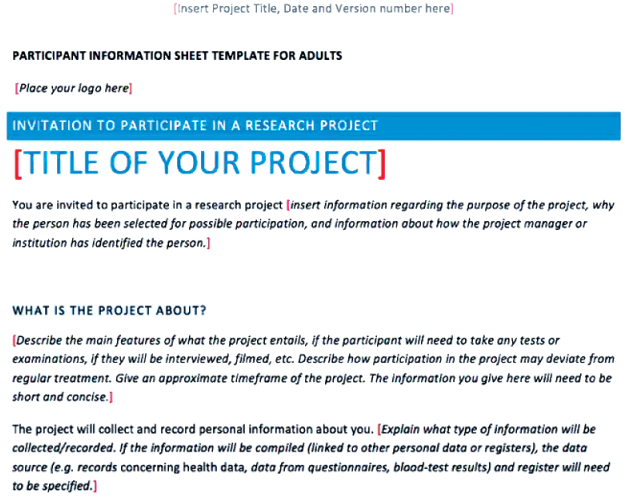
Important elements of the Informed consent:

The doctor has to make sure that the patient:

- ✔ Has the capacity to understand the project
- ✔ Is not under pressure
- ✔ Understands that participation is voluntary
- ✔ Is fully informed – also orally
- ✔ Has sufficient time to consider participation and discuss with family or caregivers

The patient information and consent form

- ✔ **Written and oral information**
- ✔ **Why have you been selected?**
- ✔ **What is the project about?**
- ✔ **Foreseeable risks and benefits**
- ✔ **Voluntary participation and option to withdraw consent**
- ✔ **What will happen to my data?**
- ✔ **Approval of the project**
- ✔ **Contact information**



[Insert Project Title, Date and Version number here]

PARTICIPANT INFORMATION SHEET TEMPLATE FOR ADULTS

[Place your logo here]

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

[TITLE OF YOUR PROJECT]

You are invited to participate in a research project *[insert information regarding the purpose of the project, why the person has been selected for possible participation, and information about how the project manager or institution has identified the person.]*

WHAT IS THE PROJECT ABOUT?

[Describe the main features of what the project entails, if the participant will need to take any tests or examinations, if they will be interviewed, filmed, etc. Describe how participation in the project may deviate from regular treatment. Give an approximate timeframe of the project. The information you give here will need to be short and concise.]

The project will collect and record personal information about you. *[Explain what type of information will be collected/recorded. If the information will be compiled (linked to other personal data or registers), the data source (e.g. records concerning health data, data from questionnaires, blood-test results) and register will need to be specified.]*

The above is a template to make sure that the clinician covers everything (used by the Ethics Committee in Norway).

- ✔ It must explain why the patient has been selected for the study (inclusion/exclusion criteria in a study)
- ✔ The administration of the new treatment - via tablet, injection etc.
- ✔ The risks and benefits of participating
- ✔ What it means to say no.
- ✔ Voluntary withdrawal at any time.

The information on sharing of data in the informed consent is really quite exhaustive due to the data protection laws. This is especially important in international multicenter trials where sharing of data is vital, and personal data must be protected. Projects require approval from both national and local authorities.

The patient's contact person is usually the leading physician at the site.

Inclusion criteria are all set by the lead group and the investigator of the trial.

The informed consent should be written in lay language and include the endpoints of the trial. Although the number of pages should be limited to 10 according to the ethics committees in Norway, there are often many more pages.

The patient needs sufficient time to read it, and finally it should be dated and signed both by the patient and the doctor, and the patient should be given a copy of the signed form.

Examples of inclusion/exclusion criteria from the PRIMA trial:

Main Inclusion Criteria:

- ✔ Patient must have histologically confirmed, advanced (FIGO Stage III or IV) high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first line platinum-based chemotherapy (neoadjuvant or adjuvant)
- ✔ Patient must have clinical complete response or partial response following completion of chemotherapy course.
- ✔ All Stage IV patients are eligible, irrespective of residual disease, after primary or interval debulking. Stage III patients are required to have visible residual disease after primary surgery. Patients with inoperable Stage III and IV disease are eligible
- ✔ Patient must agree to undergo central tumor HRD testing
- ✔ Patients of childbearing potential must have negative pregnancy serum test within 72 hours of being dosed
- ✔ Patient must be randomized within 12 weeks of the first day of the last cycle of chemotherapy

Main Exclusion Criteria:

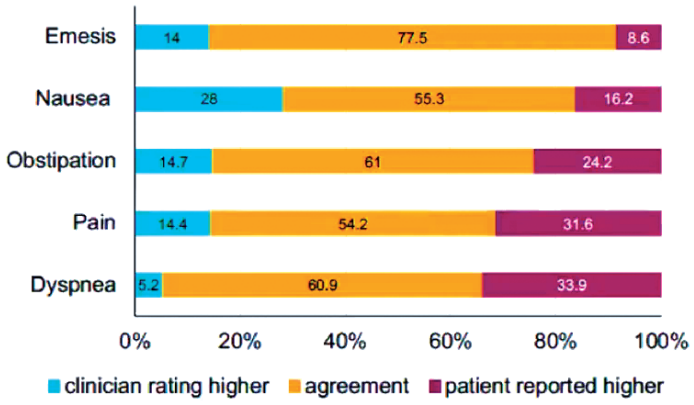
- ✔ Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer
- ✔ Patient has undergone more than 2 debulking surgeries
- ✔ Patient is to receive bevacizumab as maintenance treatment
- ✔ Patient is pregnant, breastfeeding, or expecting to conceive children, while receiving study treatment and for 180 days after the last dose of study treatment
- ✔ Patient has had prior treatment with a known PARP inhibitor
- ✔ Patient has been diagnosed and/or treated for any invasive cancer (other than study disease) less than 5 years prior to study enrollment.

Source: clinicaltrials.gov

Patient Reported Outcome - PRO

Means what it says. The patient is reporting the outcome as he/she experiences it.
It actually compares quality of life from two perspectives – the doctor and the patient
Doctors tend to underestimate toxicity. PROs are now an established part of a clinical trials.

Quality of life and side effects



- ✔ **Clinicians and patients may not agree on symptoms experienced during cancer treatment**
- ✔ **Even less agreement in subjective "non-measurable"symptoms**

Courtesy Dr. Hilpert/AZ/MSD Greimel et al Support Cancer Care 2011 Sep; 19 (9) 1421-7

Vocabulary:

Emesis = vomiting
Nausea = feeling of having to vomit
Obstipation = bad case of constipation
Dyspnea = shortness of breath

This table shows that clinicians and patients do not agree on symptoms experienced during cancer treatment – especially when it comes to pain and dyspnea. There are, however, a large orange area in the middle where they do agree. The results are a summary from three large ovarian cancer trials.

Assessment of toxicity in a clinical trial

- ✔ **Assessed by the treating physician**
- ✔ **Objective perspective**
- ✔ **Any abnormal clinical finding temmporally associated with the use of a therapy for cancer, causality is not required**
- ✔ **Graded according to the „Common Terminology Criteria for Adverse Events" (CTC AE)**

TOXICITY ASSESSMENT

As you will see from the slide toxicity in a clinical trial is graded according to CTC AE in 5 different grades of severity.

The assessment of toxicity in a clinical trial is related to the treatment but is not necessarily associated with the treatment. However, all types of toxicity need to be reported.

GRADES

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for eaxh Ae based on this general guideline:

Grade 1 Mild: asymptomatic or mild symptoms, clinical diagnostic observations only, intervention not indicated.

Grade 2 Moderate: minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalizaton indicated, disabling, limiting self care ADL**.

Grade 4 Life-threatening consequences, urgent intervention indicated,

Grade 5 Death related to AE.

PROM (Patient Related Outcome Measure)

Is rated by the patient herself.

It concerns the way she feels during treatment – not only shortness of breath or bowel movement, but also social function and social life.

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 the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in you initials: |_|_|_|_|

Your birthday (Day, Month, Year) |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year) |_|_|_|_|_|_|_|_|

		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 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

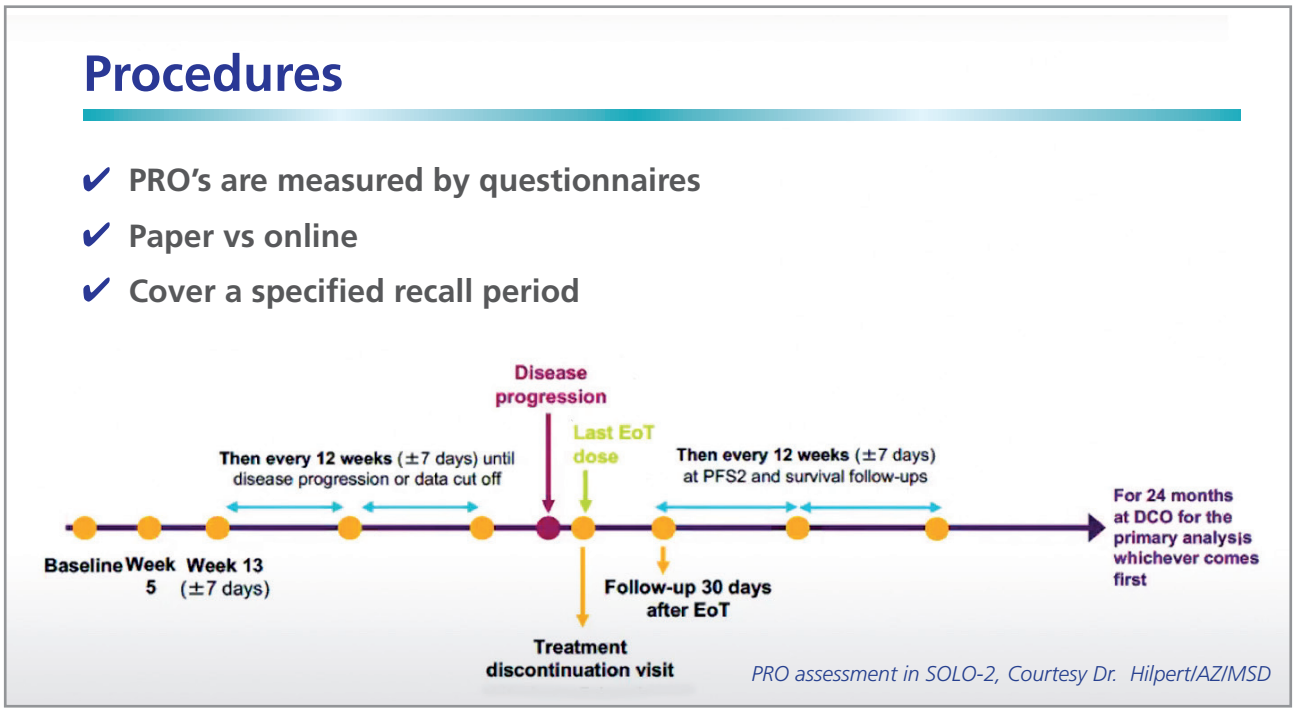
Example of a PROM

There is also a depression and anxiety questionnaire. Questionnaires need to be validated. You can read more about questionnaires and validation at **https://www.eortc.org/at eortc.com**

Now questionnaires need to be more specific. Why is that? Because immunotherapy has completely different side effects and also side effect that may arise at a later point in time. We need to capture the symptoms of the patient.

Efficacy and side effects play a much bigger role than they did 20 years ago.

Besides efficacy and the costs of the drug, side effects and quality of life play an important part in the approval of the drug.



Acronyms:

Eot = End of treatment
DCO = Data Cut Off

Another example of a PRO as a genetic instrument and a categorized scale.

A timeframe is often given for answers e.g., last week or last 2 weeks. It requires that the patient is IT literate as PRO's are often filled out online.

The example above is from the SOLO 1 study. Notice how often data are collected.

This PRO does not stop at disease progression. It continues. We should not burden the patients with too many questions - especially when they are having a relapse of their disease.

When the patient is in maintenance treatment, which is the case on the slide above, and has a treatment-free period where she can return to her ordinary life, it is likewise important not to burden her with too many questions.

Do we measure what matters? Role of patient organizations

- ✔ **Evaluating and reviewing PROMs**
- ✔ **Identifying the need for PROMs**
- ✔ **Developing and evaluating conceptual and/or theoretical framework**
- ✔ **Providing concepts through PRO awareness**
- ✔ **Endorsing PROMs**
- ✔ **Highligting needs**
- ✔ **Reviewing reporting of results**

According to the presenter, it is important to get patient networks like ENGAGe and patient organisations involved when the trial is being designed.

- ✔ We can help in the design of a PROM.
- ✔ We can help evaluate and review PROM's.
- ✔ We can help raise awareness of PRO's.

We can also help to communicate to the patients that they need to provide the data. Make them aware of the value of it. This is where patient organisations could play an important role

It is also essential to report the results of a PROM to lay persons and the public.

PRO's for Palliative care was brought up – Is the patient satisfied with the care she is given? Is what doctors think the patient needs, actually what the patient prefers?

Sometimes older questionnaires are used together with PROMs. This could create the problem of too many questions to answer for the patients. Maybe we should try to have the older questionnaires up-dated.

ENGOT and ENGAGe ought to work on new forms of scoring. The patients side effects and quality of life need to be scored and updated in a much more personal and interactive way – preferably online. This is a hot topic – we need new versions of questionnaires.

This is a topic where the patient participants in the clinical trials project could really contribute with important insight. Let's get the patient perspective into the questions asked in PRO's and PROM's.

This could really make a difference to many patients in a clinical trial and make patients' view of side effects correlate more with their doctors' view on the same side effects.

Terminology

A list of the most common terms in a clinical trial with an explanation of what they mean. The list is not exhaustive but will prove helpful in most clinical trials.

Adverse events (AEs)—any unfavourable or unintended sign or symptom (e.g., laboratory finding) that occurs while the patient is enrolled in a clinical trial.

Adverse events of special interest (AESIs) —may be serious or not; is of special interest to the investigator and the sponsor of a clinical trial.

Alpha error/Type I error—when a trial deems a drug or therapy not effective but in fact it is.

Beta error/Type II error—when a trial deems a drug or therapy effective, but it is not.

Clinical trial—A clinical trial is a research study to answer specific questions about vaccines, new therapies, or new ways of using known treatments. (definition from clinicaltrials.gov)

Disease-free survival (DFS)—the time from the treatment ending until the patient has additional symptoms or relapse or death.

Disease control rate (DCR)—proportion of patients who present stable disease as their best overall response

Dose-limiting toxicity (DLT)—the amount of a drug or therapy at which the side effects are serious enough that no additional amount can be given

Duration of response (DOR)—time from the initial tumour response (either complete or partial) until tumour progression

FIGO - The FIGO staging systems are determined by the International Federation of Gynecology and Obstetrics.

IN GENERAL, THERE ARE FIVE STAGES:

- ✔ **stage 0:** carcinoma in situ (common in cervical, vaginal, and vulval cancer)
- ✔ **stage I:** confined to the organ of origin
- ✔ **stage II:** invasion of surrounding organs or tissue
- ✔ **stage III:** spread to distant nodes or tissue within the pelvis
- ✔ **stage IV:** distant metastasis(es)

Hazard ratio: A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups. Source: National Cancer Institute

Kaplan-Meier method: The Kaplan–Meier estimator, also known as the product limit estimator, is a non-parametric statistic used to estimate the survival function from lifetime data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment. *Source: Wikipedia*

MTD (maximum tolerated dose)—the maximum a patient can tolerate, on average, as determined by a clinical trial.

Objective response rate (ORR)—proportion of patients who have a tumour-size reduction of a predefined amount; often used as an endpoint.

Overall survival (OS)—the length of time a patient lives following diagnosis or start of treatment (used to measure success of drugs and therapies)

PFS (progression-free survival)—the time from the treatment until the patient has no worsening symptoms of the disease (progression) or death; can be a surrogate endpoint for overall survival

Prospective trial—a trial in which the data from patients are collected before and up to the time when the patients display an outcome.

P Value—$P > 0.05$ is the probability that the null hypothesis is true. A statistically significant test result ($P \leq 0.05$) means that the test hypothesis is false or should be rejected. A P-value greater than 0.05 means that no effect was observed.

Randomised controlled trial—a trial in which patients are randomly assigned to one or more groups and each group is given different treatment and results are then analysed and compared between groups.

RECIST 1.1—Response evaluation criteria in solid tumors

The RECIST specification establishes a minimum size for measurable lesions, limits the number of lesions to follow and standardizes unidimensional measures. *Source: Wikipedia.org*

Retrospective trial—a trial in which the data of patients who have already achieved an outcome are analysed.

Serious adverse events (SAEs)—an adverse event that results in death or illness requiring hospitalisation.

Standard of care (SoC)—the level of treatment that a patient should receive for a particular medical situation.

Translational research—research to create new therapies and procedures, building on existing knowledge.

List of acronyms

AEs = Adverse Events

AESI = Adverse Event of Special Interest

CBR = Clinical Benefit Rate

CR = Complete Response

CTC AE = Common Terminology Criteria for Adverse Events

DCO = Data Cut Off

DCR = Disease Control Rate

DFS = Disease-free Survival

DLT = Dose Limiting Toxicity

DOR = Duration of Response

EoT = End of treatment

GCP = Good Clinical Practice

HRQOL = Health-related quality of life

MTD = Maximum Tolerated Dose

ORR = Objective Response Rate

OS = Overall survival

pCR = pathologic Complete Response

PD = Progressive Disease

PFS = Progression-free Survival

PR = Partial Response

PRO = Patient Reported Outcome

PROM = Patient Reported Outcome Measures

QoL = Quality of Life

RECIST 1.1 = Response evaluation criteria in solid tumors

RCT = Randomised Controlled Trial

SAEs = Serious Adverse Events

SD = Stable Disease

SoC = Standard of Care

SUSAR = Suspected Unexpected Serious Adverse Reaction

Summary of the webinars

by Beth Green

Clinical Trials: Basics

Clinical trials are needed to obtain the best evidence that a drug is effective before it is set as the standard of care for patients.

First, researchers look at the effects of drugs on cells in a lab. Once efficacy is shown in that step, the researchers move to animal experiments. It is not always possible to perform animal experiments for all new drugs/therapies, for example, with immunotherapy drugs. The following step is to launch a clinical trial that enrols humans. Phase I, II, and III trials, that enrol larger and larger numbers of patients, as well as randomised and comparative trials, in order to provide further evidence as to whether a drug should be used as the standard of care.

Each of the levels of investigation in a clinical trial adds to the proof that the drug works—and further defines for which patients and for which tumours or biomarkers the drug is most effective. One doctor noticing that his group of 100 patients had similar results is evidence but probably not enough to persuade the field to change the standard of care; a randomised trial comparing data from thousands of patients from different institutions is even more powerful evidence.

TYPES OF ERRORS—may be due to trial design; (probability calculated as a percentage)

Alpha error/Type I error—when a trial deems a drug or therapy not effective but in fact it is

Beta error/Type II error—when a trial deems a drug or therapy effective, but it is not

COMPREHENSION CHECK:

- ✔ Why are clinical trials needed?
- ✔ What are the differences between phases of clinical trials?
- ✔ How do clinical trials progress from ideas to the drug being ready to be included in the standard of care?
- ✔ What is 'evidence' in a clinical trial?

TYPES OF CLINICAL TRIALS

Phase I—focuses on the maximum tolerated dose of a drug; small number of patients studied (sometimes combined with Phase II)

Phase II—focuses on activity of the drug against the cancer; medium number of patients studied (sometimes combined with Phase I)

Phase III—focuses on comparing the standard of care against what is being studied; tries to determine efficacy of a drug; involves large number of patients; and is the most powerful for being able to register a new drug

Adaptive trial—a trial in which the parameters of the trial are adjusted (adapted) as the investigators record their observations; can incorporate different patient types and different tumour types

Basket trial—a trial in which all patients get the same therapy that targets a specific mutation, though they may have different types of cancer

Umbrella trial—a trial that focuses on a specific type of tumour, possibly with different mutations

Endpoints

Every clinical trial sets objectives. These objectives must be concrete, easy to understand, and clearly specified; for example, the objective could be to determine the safety, activity, or efficacy of a drug or therapy. Clinical trials typically have both primary and secondary objectives.

How do we know when the objective has been met? We use endpoints. Endpoints are the quantitative measurement or data point needed to meet the objective of the trial; the outcome used to determine the end of the trial: dose-limiting toxicity, response, patient survival. Endpoints can be binary (yes/no), ordinal, continuous, or time categorical.

Clinical endpoint—Direct benefit to the patient, i.e., decreased pain

Surrogate endpoint—other indicators of if the treatment is working, i.e., decreased tumour size

COMPREHENSION CHECK:

- ✔ What is an endpoint in a clinical trial?
- ✔ What is the difference between a clinical endpoint and a surrogate endpoint?

Quality of Life

During a clinical trial, it is important to assess the patients' quality of life. Quality of life is measured with several different tools and reported with a variety of data points. Patient-reported outcomes are collected through questionnaires and surveys, often at specific time intervals. The questions asked are about symptoms that affect quality of life, though some of them can be difficult to measure. Though subjective, the collection of this data is quite important for ensuring the patient perspective is recognised in the trial results; for example, the patient may report higher pain levels or other intangible data points that are difficult for the clinician to simply observe. Other patient perspectives offered through self-reported quality of life surveys cover measures of depression, anxiety, and satisfaction of care.

The surveys and questions used to collect quality of life data can be online or on paper. They are called 'tools', and designing accurate, efficient and useful tools is an ongoing process. Researchers try to find a balance between creating tools that accurately gather data and not overwhelming the patient with too many data points to consider, as lengthy questionnaires may reduce the number of patients who fill in everything.

COMPREHENSION CHECK:

- ✔ How is quality of life measured?
- ✔ What type of patient perspectives are collected in clinical trials?

Informed consent

Before a patient takes part in a clinical trial, the doctor and patient go through informed consent. Informed consent is the process in which the medical team informs the patient about the risks and benefits of the treatment, about alternative treatments and their risks and benefits. The patient decides whether or not to agree to participate based on this information. The doctor or medical team also has the obligation to assess whether the patient has fully understood this information. The patient both gives consent orally to their doctor and also signs a written informed consent document.

There should be no surprises for the patient during the trial: all of the procedures and steps of their participation in the trial should be outlined in writing before the patient is enrolled. In addition, the contact information for the principal investigator of the study should be clear and accessible for patients, in case they need additional information.

A patient's participation in a clinical trial is always voluntary; a patient can withdraw at any time—either from the procedures in the trial or from the collection of the data. In the study design, the researchers must make sure to guard patient privacy and keep patient data private. Any data shared among centres, for example, will be anonymised. At the same time, not every patient is suitable for inclusion in every trial about their disease. The principal investigator of the study sets out clearly what are the criteria for inclusion and exclusion before any patients are enrolled.

COMPREHENSION CHECK QUESTIONS:

- ✔ What is informed consent?
- ✔ Do patients have contact information for the trial organisers?
- ✔ Can a patient withdraw from a clinical trial?

ENGAGe
ESGO European Network of Gynaecological Cancer Advocacy Groups

ENGOT
European Network of Gynaecological Oncological Trial groups

ESGO
European Society of Gynaecological Oncology