

# memo – inOncology SPECIAL ISSUE

Medical Education

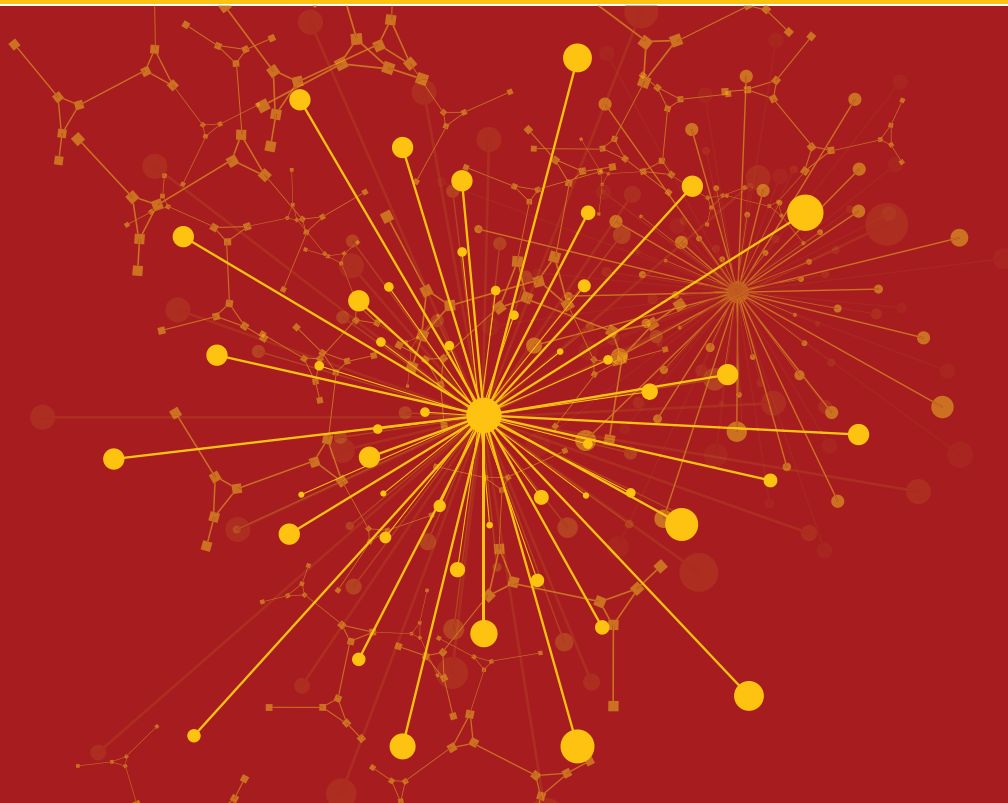


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## FUNDAMENTALS OF DESIGNING CLINICAL TRIALS

Part 1: Biomarkers in oncology trials

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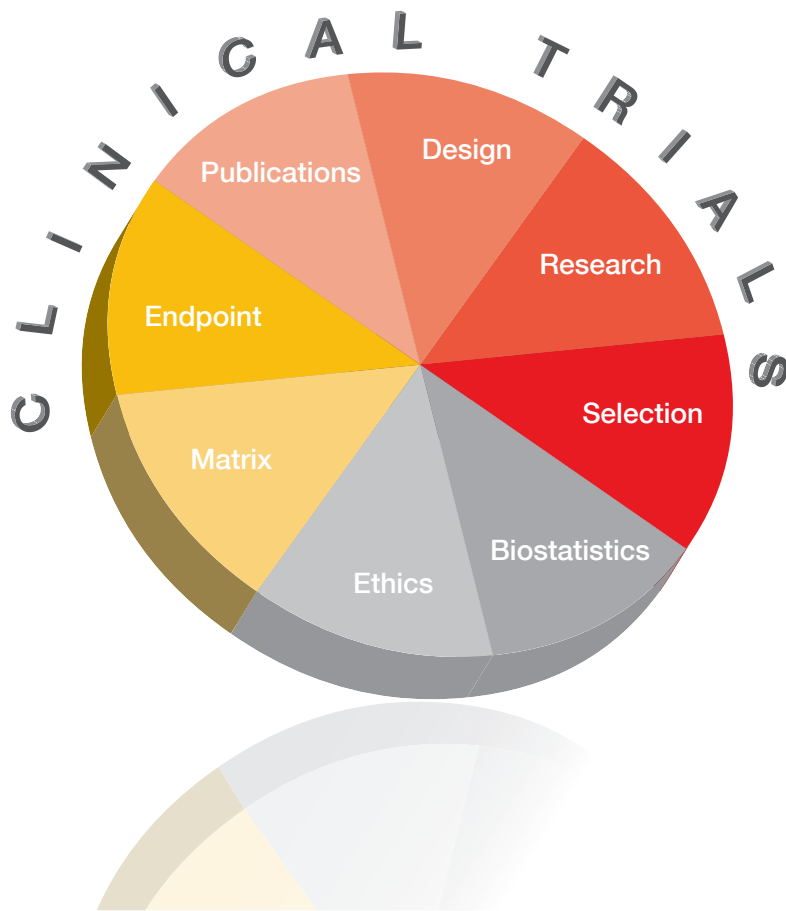


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## Preface

### Dear Colleagues

In this special issue related to biomarkers and ethics in oncology trials, international experts have provided their perspectives on the most important elements related to their successful design, conduct and implementation of their results into clinical practice.

Dr. Silvia Novello and myself review how there has been a renewed optimism in achieving major improvements in the clinical care of patients based upon the identification and use of biomarkers that relate to the underlying biology of cancer. However, the identification and use of such biomarkers requires that a series of steps be fol-

lowed to ensure that they are valid and useful. Negotiating the regulatory pathways is not always easy, and both the novice and more experienced clinical researchers are guided through the necessary steps in this overview.

Undertaking human research goes hand in hand with ensuring that people are respected and protected from unnecessary and avoidable risk of harm. The benefits should in all instances over-ride the harms, but in cancer where patients are often at high risk of death and are dependent on care, the balance is sometimes harder to strike, and patients are willing to take risks that they may not in other medical settings. In my article on ethical considerations, I steer a path through the issues that will confront those engaged in biomarker-driven oncology trials and provide a practical approach to ensuring that the highest ethical standards are met without creating



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unnecessary burdens or hurdles to undertake potentially life-saving research.

We commend this paper to you and hope that it provides a succinct, useful and entertaining guide to undertaking research in this exciting area.

# Biomarker-based clinical trials: study design and regulatory requirements

## Introduction

Due to the recent developments in the field of molecular diagnosis, it has become evident that there is no such entity as cancer per se, as there are considerable biological differences even within a particular anatomical subtype. Genomic characteristics do not only help to better define tumor subtypes, but frequently they provide the opportunity to target these subtypes as well. This can thus lead to the development of therapeutic approaches that surpass conventional treatments in terms of efficacy and tolerability. The International Cancer Genome Consortium (<http://icgc.org/>) has made it its task to generate comprehensive catalogues of genomic abnormalities (somatic mutations, abnormal gene expression, epigenetic modifications) in tumors from 50 different cancer types and/or subtypes across the globe, and to make these data publicly available. This is one of the largest natural history projects of the last decades.

The availability of rapid and relatively cheap molecular profiling underpins translational research, enabling the transition from preclinical insights to global implementation of testing of new treatments in clinical trials. The inclusion of companion biomarkers has become mandatory in all new drug trials that are conducted for targeted therapies in the oncological field. Whilst the term 'biomarker' encompasses a broad range of parameters that go beyond the molecular characteristics, it has become most closely associated with genomics and other '-omic' analyses.

## Definition

In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". This means that biomarkers represent a variety of param-

eters including, but not limited to, the genomic characteristics. **Table 1** provides some examples of biomarkers. Even the diagnosis itself, or the histology of the tumor, count as biomarkers, as well as patient age and patient sex. Drug metabolism is an important aspect too, although this is often overlooked. With respect to pharmacokinetics, potential biological markers include drug absorption, metabolism, distribution, and excretion. The differences between patients and their ability to break down drugs (i. e., fast or slow metabolizers) can be crucial for bioavailability and toxicity. Pharmacogenomics, which evaluates the role of a patient's genetic set-up in their responses to treatments, has risen to great importance. Genomic markers are targeted directly by certain therapies, and can influence their effectiveness.

## Prognostic and predictive biomarkers

While prognostic biomarkers hint at the likely outcome of a patient with a particular disease regardless of their treatment, predictive biomarkers provide information on whether that patient will respond to a certain agent. Some markers provide both of these functions. For instance, estrogen receptor positivity in breast cancer patients indicates a favorable prognosis (providing prognostic information); at the same time, it means that the patient will probably respond to

endocrine therapy (providing predictive information).

## Surrogate biomarkers

In early phase trials, surrogate biomarker endpoints can allow the determination of treatment effects at earlier times than the ultimate clinical endpoint of interest, such as progression-free survival or overall survival. Valid surrogate biomarkers have both prognostic and predictive properties, as they also demonstrate mechanisms of molecular action. However, the question remains whether the treatment effect on the biomarker reliably predicts the treatment effect on the clinical endpoint.

## Take home message

Biomarkers are biological markers of any type that are objectively measurable. Apart from molecular characteristics, these include parameters such as blood values, pharmacokinetics, and imaging. While prognostic biomarkers are indicative of the outcome of a patient with a particular disease, predictive biomarkers provide information on whether a patient will respond to a certain agent. Surrogate biomarker endpoints enable the evaluation of treatment effects earlier than clinical endpoints in early phase trials.

TABLE 1

### Some examples of biomarkers

Blood	Cholesterol and LDL:HDL ratio
	Blood glucose
	Circulating DNA
Blood pressure	
Weight loss	
Electrical activity of the brain	
Imaging	PET/CT- RECIST criteria
Tissue biomarkers	ER/PR/HER2
	KRAS, BRAF, ALK

## Use of biomarkers in trials

In clinical trials, biomarkers serve a range of practical uses:

- Screening of patients for eligibility
- Stratification into subgroups
- Monitoring of responses
- Correlative studies for future reference

Many study protocols include the collection of additional samples that are not necessarily used for the endpoint of the specific trial, but rather for purposes of design of future studies. Also, studies can be designed with a view to re-analyzing the dataset later on in the light of new information that has been revealed by further research (e. g., new markers or genes).

Ideal markers require minimally invasive sampling, are reliable (i. e., internally consistent), cheap, and highly sensitive and specific. Re-biopsy is frequently recommended in the advanced setting, as clonal evolution can lead to differences in molecular characteristics between the original tumor and its metastases, and even between metastatic lesions within a given patient. Among other uses, biomarkers can serve as indicators of futility that alert the researchers to the necessity of early study termination; for instance, if the biological effect is below the maximally tolerated dose.

### Basket and umbrella trials

The emergence of genomic biomarkers has prompted the development of trials that are not restricted to certain anatomically defined cancer types. In these so-called 'basket trials', a particular mutation is targeted that occurs in tumors of different origins. 'Umbrella trials', on the other hand, assess a variety of drugs usually in one cancer type that has different molecular alterations. Here, patients with a single tumor type or histology are enrolled, but multiple sub-trials evaluate targeted therapies within molecularly defined subsets. The implementation of basket trials and umbrella trials poses specific challenges both in terms of recruitment, since the numbers of eligible patients falls with increasing use of molecular inclusion criteria, and also with needing to create trials that require cooperation from pharmaceutical

drug companies that might have competing agents in their pipeline.

### Take home message

Ideally, biomarkers are reliable, cheap, highly sensitive and specific, and require minimally invasive sampling. Their uses in clinical trials comprise screening of patients for eligibility, enrichment, monitoring of responses, and future correlative studies. Studies can be designed with a view to re-analyzing biomarker sets later on, as new information becomes available. Basket trials encompass tumors of different origin with the same mutation; umbrella trials evaluate different targeted drugs within subsets of patients with the same tumor.

## Ethical and practical limitations

From an ethical point of view, it could be argued that molecular screening should be performed at the time of diagnosis rather than in the advanced disease stage, as this can enable patients to benefit from certain treatments early on. However, early testing raises financial concerns if the patient has to pay for this themselves, but also in terms of cost-benefit evaluations if the government pays. Another ethical conflict that might arise is the randomization of patients into the control group. Many patients decline this, in the knowledge that they might be denied an enormously effective treatment.

Practical problems also arise because biomarkers tend to be imprecise. More widespread genomic analysis shows that the penetrance of genes is often incomplete, and some major confounders are awaiting improved understanding, such as the microenvironment. For example, the bacteria in the gut are known to affect the way patients respond to treatments. Also, further research is required regarding putative interactions between the targeted pathways and the immune system. Moreover, objective measurability, as mentioned in the "Definition" section above, can pose problems in clinical practice. While the presence of mutations is assessed on a yes-or-no ba-

sis, immunohistochemistry uses ranges of values that often elude precise quantification.

It can be assumed that data from phase IV registries will accumulate in the future and will shed light on these issues. Pharmaceutical companies are obliged to set-up these registries, which correlate the presence of biomarkers to clinical outcomes.

### Take home message

Ethical concerns relating to biomarker studies include early molecular screening and randomization into the control group. Incomplete penetrance of genes and confounders such as the microenvironment or unknown interactions between pathways and the immune system are limiting factors.

## Validation of prognostic and predictive biomarkers

From the registration point of view, biomarkers need to be valid and reproducible. Regulatory authorities are required to ensure that standardized tests are available for biomarker testing. The average pathology laboratory should be able to deliver them in a rapid, cheap, and effective manner. Equally important for registration, the biomarker needs to be included in any reimbursement schedule.

Validation of biomarkers in clinical trials includes:

- Proof of concept;
- Experimental validation;
- Analytical performance validation;
- Protocol standardization.

### Proof of concept

A classic example of proof-of-concept assessment is the identification of the *KRAS* mutational status as a predictive marker in the context of anti-EGFR antibody therapy. *KRAS* mutation has been established as an important marker in colorectal cancer (CRC) since the 1990s. The *KRAS* protein regulates downstream proteins in the EGFR signaling pathway that are associated with tumor survival, angiogenesis, proliferation, and metas-

**TABLE 2**  
**Analytical validation**

Reproducibility (day to day, performer to performer, batch to batch)
Linearity
Recovery
Specificity
Cross-reactivity of related substances
Interference of rheumatoid factor and human anti-mouse antibodies
Monitoring of calibration curves
Precision/ accuracy
Detection limit
Acceptance criteria for assay runs (internal quality control)
Normal values, cut-off values
Biological variation, age, and gender

**TABLE 3**  
**Clinical validation**

Retrospective analysis of 'all-comer' trials
Retrospective analysis of 'biomarker-selected' trials
Prospective analysis of 'biomarker-selected' trials
Prospective analysis of 'biomarker-selected' vs. 'standard comparison' trials
Prospective analysis of 'predictive biomarker validation' trials

tasis. Whereas wild-type *KRAS* denotes preserved function of the protein, mutant *KRAS* is indicative of persistent growth stimulation. This mutation is found in one third of CRC patients.

The primary analysis of the randomized, phase III NCIC/AGITG CO.17 trial, which did not stratify for *KRAS* mutation status, yielded no clinically relevant advantage of the anti-EGFR antibody cetuximab over placebo in patients with advanced CRC [1]. According to the *post-hoc* analysis, however, when mutations status was considered, there was a distinct difference between the two treatment arms [2]. In *KRAS*-mutant patients, cetuximab did not show any benefit, whereas those with *KRAS* wildtype obtained significant overall survival advantage when treated with this antibody.

#### Experimental validation

Once biomarker development reaches the level of the diagnostic laboratory, very high standards are required. Experimental validation includes the two elements of analytical and clinical validation (**Tables 2 and 3**) [3]. Clinical val-

idation should ideally be conducted in a prospective study, rather than in the retrospective setting, as biomarker analysis on the basis of existing data from randomized controlled trials has several drawbacks [4]. In many cases, the original study will not have been powered for a correlative science endpoint, and tissue has not necessarily been obtained in all of the randomized patients. Outcomes obtained in a retrospective setting are generally considered hypothesis-generating and need to be confirmed in prospective studies.

Gains in efficiency depend on the marker prevalence and the relative efficacy in biomarker-positive and biomarker-negative patients. Trials with an enrichment design only enroll patients who are likely to respond. The use of an enrichment design improves efficiency (**Table 4**) and is also an important factor with regard to cost [5]. However, exclusion of those patients who are not likely to benefit implies the need to understand the scientific basis of the targeted agent, and statistical simulations should have demonstrated improved efficacy through enrichment.

#### Analytical performance validation

Analytical performance validation encompasses clinical laboratory measurements with the aim of assessing the analytical performance of various biomarker assays. For *KRAS* mutation testing, seven different methodologies were compared in 2009 [6]. Today, next-generation sequencing is increasingly becoming the standard technique as part of a much broader panel to examine mutations across several targetable pathways.

#### Protocol standardization

With respect to *KRAS* testing, data from the CRYSTAL study suggested that extended *RAS* testing is more appropriate, as mutations in various *KRAS* exons as well as in *NRAS* exons equally affect outcomes [7]. Today, all-*RAS* mutation testing is recommended by the guidelines [8].

#### Take home message

Companion biomarkers are an important part of drug registration and reimbursement. From the point of view of regulatory authorities, biomarkers should be valid and reproducible, and laboratories should be able to provide rapid and cheap biomarker testing. Validation of biomarkers in clinical trials includes proof of concept, experimental validation (including analytical and clinical validation), analytical performance validation, and protocol standardization. Clinical validation should be conducted in a prospective setting. The use of an enrichment design improves efficiency.

#### Approval of biomarker studies: regulatory requirements

Regulatory authorities are generally perceived as being difficult and bureaucratic, but they serve an important function in terms of protecting and promoting public health. They ensure quality, safety, and efficacy of treatment. Also, they provide adequate and appropriate information for both patients and physi-



**TABLE 4**  
**Improvements in efficiency through trial enrichment design**

Prevalence of biomarker-positive patients (%)	Relative efficacy (%)	Efficiency gain (times)
25	100	16
25	50	2.5
50	100	4
50	50	1.8
75	100	1.8
75	50	1.3

cians. Naturally, their approach is conservative and careful, as mistakes on their part can have vast consequences. From the researcher's point of view, being empathetic to their objectives and complying with them will alleviate co-operation and reduce conflict. The instructions of the regulatory authorities should thus be followed closely.

The approaches to regulation vary worldwide. For instance, the Japanese regulatory authorities believe that clinical data from foreign patients are of limited applicability to Japanese patients, which is why they require stand-alone development programs. However, there are many similarities. Regulatory authorities generally run comprehensive websites that provide useful information on biomarker qualification, such as numerous academic inputs into the optimal study design. Templates where information can be added in to a prepared structure are provided at the US Food and Drug Administration (FDA) website ([www.fda.gov](http://www.fda.gov)). At the European Medicines Agency (EMA) website

(<http://www.ema.europa.eu/ema/>), researchers have the opportunity to receive comments from member states as part of the centralized approval procedure (Figure 1).

#### Review and protocol

The regulatory authorities are still assessing the optimal ways to incorporate biomarkers into clinical trials. For the future, it can be expected that countries will increasingly cooperate in this respect.

At present, researchers have to provide protocols that detail all of the proceedings planned for the study, as well as the quality assurance measures. In most cases, the rationale for a trial will be supported by experimental findings provided by other study groups. Only a minority of researchers can provide their own laboratory data. Therefore, a detailed review of the available literature is necessary as a background statement. The FDA requires researchers to create a Context of Use Statement for Bi-

omarker Qualification, which is part of the general protocol and describes the manner of use, interpretation, and purpose of use of a biomarker in drug development [9]. Five elements of the Context of Use Statement are specifically defined (Table 5). In the context of quality improvement and quality assurance, even apparently small aspects can be of importance, such as correct handling of blood tubes or timing of assessments by a pathologist. All of these should be defined in the study protocol.

#### Take home message

On their websites, regulatory authorities provide frameworks for including biomarkers in clinical trials. Researchers are required to provide protocols that review the existing data in the literature, and that detail all of the proceedings and quality assurance measures planned for a study. An FDA requirement is the creation of a Context of Use Statement for Biomarker Qualification, which describes the manner of use, interpretation, and purpose of use of a biomarker in drug development.

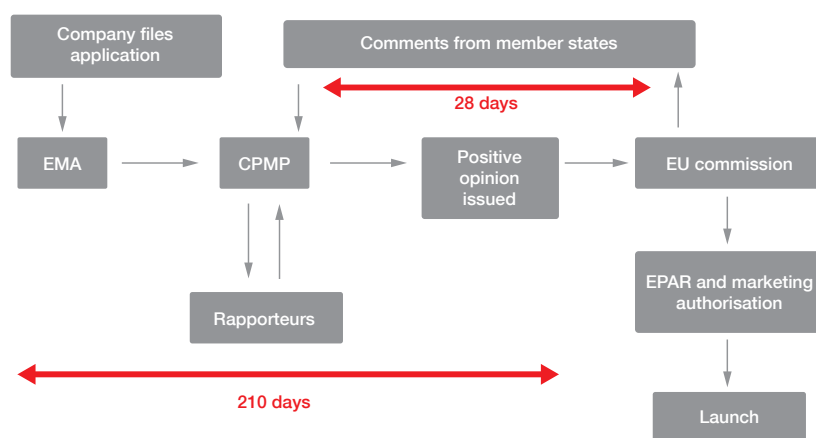
#### Translational research in NSCLC

The transformation of the management of advanced non-small-cell lung cancer (NSCLC) over the last 10 years exemplifies the magnitude of changes in treatment paradigms that can be brought about by scientific progress. Translational research has contributed greatly to each step along the way.

#### Enzyme expression as a key to efficacy

Until 2008, the choice of treatment of lung cancer patients relied mainly on differentiation between small-cell and non-small-cell histology, with doublet chemotherapy being the standard approach. Toxicity was an important determinant in any treatment decision.

At that time, the first prospective trial was conducted in NSCLC patients that contained a pre-planned analysis to evaluate histology as a possible predictive factor [10]. This showed that peme-



CPMP, Committee for Proprietary Medicinal Products;  
EPAR, European Public Assessment Report

**Figure 1:** EMA: centralized approval procedure

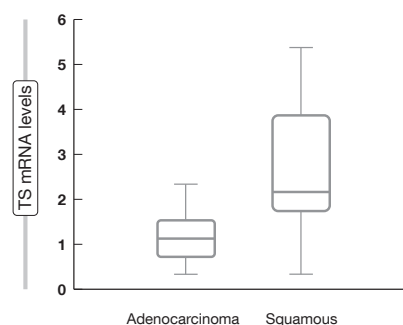
**TABLE 5**  
**Elements of the Context of Use Statement for Biomarker Qualification**

	Element	Example
1	Identity of the biomarker	Specific type of radiological examination with specific imaging modalities (e.g., MRI, PET, Doppler)
		Specific substance/ analyte in physiological fluid
		Specific genomic biomarker
2	Aspect of the biomarker that is measured, and the form in which it is used for biological interpretation	Specific aspect of radiological findings, such as lesion number, volume, diameter, area, perimeter, or other characteristics (e.g., tumor volume)
		Specific measure of organ size
		Serum level of an analyte; possibly also specified in relation to time (e.g., at a specific time, steady-state, AUC, post-treatment minus pre-treatment)
		Used in graded measurement form or after threshold categorization (e.g., change relative to a reference such as baseline, historical control, or normal range, or X-fold change)
3	Species and characteristics of animal or subjects studied	Animal species or range of species
		For each species, important characteristics (e.g., strain, age, sex, disease model, healthy)
		Human and important characteristics (e.g., age, race/ ethnicity, sex, disease, healthy, genotype, disease phenotype)
4	Purpose of use in drug development	Demonstration of absence of toxicity (non-clinical or clinical)
		Demonstration of organ toxicity without performing extensive histopathology (non-clinical biomarkers)
		Evaluation of exposure response
		Use in clinical study subject enrolment or randomization (e.g., diagnostic, enrichment, stratification)
5	Drug development circumstances for applying the biomarker	<b>Non-clinical:</b>
		Determination of “no observable adverse effect level” (NOAEL) for a specific toxicity when prior toxicology studies have not identified NOAEL with adequate precision;
		Selection of the best drug candidate among several drug candidates based upon a specific toxicity;
		Demonstration of activity of the drug on the disease pathophysiology (via an animal disease model).
		<b>Clinical:</b>
		Selection of doses to take into phase III studies (i.e., apply biomarker in dose-finding studies intended to predict efficacy);
		Ensuring patient safety in dose-escalation safety studies;
		Demonstration of activity of the drug on the disease pathophysiology (i.e., clinical proof-of-concept studies).

trexed plus cisplatin is more efficacious in patients with adenocarcinoma, while the results obtained in patients with squamous-cell histology favored gemcitabine plus cisplatin. These findings prompted a revision in the indications for pemetrexed (which is now approved for the treatment of advanced, non-squamous NSCLC) and underlined the relevance of this multidisciplinary approach to disease.

Translational research provided the rationale for the then-unusual histological stratification. It was shown that thymidylate synthase (TS), which is one of the enzymes involved in pemetrexed metabolism, is expressed to a significantly higher degree in squamous-cell carcinoma than in adenocarcinoma of the lung (**Figure 2**) [11]. Meanwhile, a meta-analysis confirmed the predictive

significance of TS expression for several endpoints (i.e., response rate, progression-free survival, overall survival) in the setting of pemetrexed-based chemotherapy in NSCLC [12].



**Figure 2:** Significant differences in the expression of thymidylate synthase (TS) in adenocarcinoma and squamous-cell carcinoma of the lung (formalin-fixed paraffin-embedded tissue)

For small-cell lung cancer (SCLC), on the other hand, the randomized GALES study revealed inferior performance of pemetrexed plus carboplatin as compared to the standard regimen of etoposide plus carboplatin [13]. These findings are in keeping with insights gained concurrently in the preclinical setting, according to which TS is highly expressed in SCLC [14].

#### Reasons for negative trial results

However, pharmacogenomic and translational research is not always successful. A testament to this is the adjuvant study landscape for NSCLC, which has been marked by a series of negative trials. Translational research can be conducted most easily in the adjuvant setting, due to the abundance of available tissue.



There are several possible reasons for this. One is the diagnostic test itself, which can be tainted by insufficient sensitivity or specificity. The TASTE trial determined the expression of the excision repair cross-complementation group 1 (ERCC1) protein using this as the biomarker in the design of the pharmacogenomics-driven trial. However, the study was stopped at 150 patients due to the unexpected lack of reliability of the ERCC1 IHC read-out, and the phase III trial was canceled. Using historical International Adjuvant Lung Cancer Trial (IALT) data, the expected and observed biomarker distribution deviated considerably from each other [15]. The choice of detection and enrichment was presumably the reason for the negative outcome in the RADIANT trial, too. The RADIANT trial compared erlotinib and placebo following complete tumor resection and standard treatment [16]. Here, the researchers used IHC and FISH to determine *EGFR* status, which was probably not an adequate technique, even though it was considered modern at the time of the design of the study.

Another reason behind negative results in translational research is the choice of only one biomarker. As a general rule, a more complete profile needs to be defined in pharmacogenomic-driven trials. A single biomarker suffices only if it is a distinct driver aberration, and the *EGFR* mutation is a good example in this context. Generally speaking, all the pharmacogenomic-driven trials conducted with only one biomarker have been negative, in both the adjuvant and the advanced settings.

Trial design can also be flawed, which makes relevant comparisons difficult. Above all, the molecular profile should be defined prior to the allocation (or randomization) of the patients to the experimental arm *versus* the control arm, as used in the design of the adjuvant ITACA trial [17]. ITACA compared standard chemotherapy *versus* pharmacogenomic-guided regimens after the assessment of ERCC1 and TS using real-time PCR, with the identification of four different profiles. ■

### Take home message

In the treatment of lung cancer, long-standing paradigms changed in 2008 with the first prospective trial that contained a pre-planned analysis for histology, which led to amendment to the approval of pemetrexed. The expression of thymidylate synthase was shown to be highly relevant for the clinical benefit derived from this treatment. Translational research has not always been successful; the reasons for negative trials have included flaws with regard to diagnostic tests, study design, methodology, and the use of a single biomarker.

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Nik Zeps

## Ethical considerations in clinical trials, and responsibilities of a principal investigator

### Introduction

Ethics can best be thought of as the moral principles that underpin good behavior. However, how this is defined is open to wide interpretation, and de-

pends on factors such as societal norms and religion. Thales of Miletus (624 BC – 546 BC) advised his contemporaries to avoid doing what they would blame others for doing, and similar expressions of this concept abound throughout a range

of moral philosophies. In medicine, the concept of non-maleficence (i.e., not harming the patient) is established as a pillar of physician behavior.

However, the distinction between what is good and bad is not always clear,

and an example of this in medicine is when doctors might induce serious adverse events in a patient through toxic treatments for their incurable cancer, which would be objectionable in circumstances that are not life threatening. Balancing the risk of harm with the potential benefits requires careful evaluation. This is especially the case where there is controversy over the evidence of benefit, or where an individual is being asked to expose themselves to harm for no personal advantage, but only to provide information of benefit to the community if a treatment is successful. In this instance, it is especially important that patients who are involved in clinical trials are not used as a means to an end. It is particularly important to evaluate any proposed research project in light of the actual harm that might arise, and also to ensure that people are not included for reasons that are not in their best interest. Any competing interests of researchers must be disclosed and weighed up when determining whether they might have vested interests in including patients in trials that pose personal risk of harm to them.

Benefits and risks to the wider community should be taken into account as well. For instance, relatives have a right to know about genetic abnormalities identified in a patient, such as *BRCA* mutations, although this can also be perceived as potential harm for a person not directly involved in the research if it causes anxiety and they need to undergo invasive procedures in light of the knowledge arising from a study that they were not a part of.

Any clinical trial is preceded by an application for ethical approval of the research, which must be obtained by the investigator before the start of the project. In this document, the research-

ers are required to explain how they are going to ensure the best interests of the patient *versus* their own competing interests. The application should be self-explanatory and self-sufficient, and should provide a detailed evaluation of any risks and how they will be managed and reduced. Institutions have different requirements regarding applications, but in general, they require a description of the study, a consideration of the ethical issues, and examples of the advertising materials, participant information sheets, and consent forms used. Also, details about how the safe conduct of the study will be monitored generally has to be provided, as well as who will review the data to determine whether early stopping of the trial is necessary if it proves useful or futile at an earlier stage than that defined in the study protocol.

### Moral-ethical codes

A number of guidelines define appropriate behavior in the context of medical research, and almost all contemporary documents have their origins in the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/>), which was developed by the World Medical Association in 1964, and was itself modeled on the Nuremberg Code. Those engaging in medical research should as a matter of principle familiarize themselves with the guidelines in their country, and ideally take the time to read the Declaration of Helsinki. In general, they state that the patients must give their consent to their participation in any research project; that the treating physician must take all necessary precautions to prevent or minimize the risk of harm, that any harm and inconvenience must be fully disclosed,

and that the potential participants has sufficient information and time to make valid decisions.

In addition to ethical guidelines, regulatory authorities require adherence to Good Clinical Practice (GCP) (<http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>). GCP guidelines are an international framework that encompasses standards for ensuring ethical and scientific quality in the design, conduct, recording, and reporting of trials that involve the participation of humans. GCP compliance provides public assurances that the rights, safety, and well-being of participants are protected, that the clinical trial data are credible, and that conduct is consistent with the principles that have their origin in the Declaration of Helsinki.

### Take home message

The Declaration of Helsinki is the fundamental modern statement that defines ethical standards for medical research, and most jurisdictions will have used these as the basis for their own guidelines. In addition, Good Clinical Practice guidelines serve as a guide to ensure that the research undertaken is robust and credible, without which the study would not be ethical, by definition. Simply stated, people should not participate in any research unless they have given their valid consent to do so based on sufficient information (full disclosure), which also details the risks of harm and how this will be minimized or avoided (i. e., their 'informed consent').

### Core values of clinical research

Core values of clinical research include research merit and integrity, justice, beneficence, and respect (**Table 1**).

- With regard to research merit and integrity, trials can only be considered ethical if they are designed well and have a reasonable chance of meeting their endpoints [1]. Appropriate expertise of researchers as well as sufficient resources and equipment must be in place. In addition, the researchers

TABLE 1

#### Core values in clinical research

##### Research merit and integrity

- value and validity

##### Justice

- fair distribution of burdens and benefits

##### Beneficence

- risk minimization/ justification according to potential benefits

##### Respect

- dignity of individuals – consent, privacy

have to make sure that the question that is addressed in a trial is worth asking. All of these issues need to be considered from the outset of the planning process. Basically, research should be ethical by design, and good research will be inherently ethical if it is worthwhile and the researchers abide by ethical principles in their conduct.

- The term 'justice' relates to the equal distribution of opportunities to participate in trials for certain patient groups. It also means that certain groups should not be exploited or over-sampled. For instance, patients with COPD tend to get involved in numerous trials, which can put a considerable burden on them.
- Beneficence can be thought of as the benefits that are likely to arise from the study, but also the balance of risks to the individual against the potential benefits to humanity. Even an ethical study can expose patients to risk, and this can be acceptable as long as the risk is managed effectively. Equally, not all studies will provide a benefit to participants, and indeed overselling potential benefits must be avoided, to ensure that the patients are not influenced to participate against their best interests. Evaluation of beneficence requires some sophistication, and should not be confused with risk-management strategies.
- 'Respect' refers to ensuring that the participants are recognized as autonomous beings and that they are not just a means to an end. The inherent dignity of a person is recognized through their autonomous right to decide whether to participate in any study or not, based upon sufficient information to make fair judgment. During their participation, respect can be expressed by continued commitment to ensuring that their confidentiality and privacy are not breached, and that they have a right to withdraw at any time.

#### Take home message

Clinical trials should be conducted only if the researcher knows that they are the right person for the task, that the question is worth addressing, and that the study will provide a valid answer. Ethics should not be viewed as risk management.

## Consent

Whilst consent is of significant importance, it is only one part of the ethical considerations of a study, and it does not replace ethical behavior by the investigators. Respect for patients is demonstrated through obtaining their consent, which should be voluntary and given after providing sufficient information about the risks and benefits. Consent is an expression of autonomy, but also of empowerment; it is a gift that must not be taken for granted. As trials often provide no genuine benefit for the patient, particularly in advanced cancer settings, consent can be an expression of altruism. The least appreciable argument for gaining a patient's consent is compliance with guidelines/ legal requirements, and the concept of 'getting consent' for regulatory compliance breaks the spirit of demonstrating respect for a person.

Mutual understanding is a prerequisite. It should be established that the adult patient is competent. They must be able to understand and retain the relevant information, to believe it, and to weigh it up, and thus to arrive at a valid choice for themselves. The physician should abstain from coercion of, or inducements for, the patient.

#### Pertinent versus less pertinent information

As consent forms currently often run to enormous lengths, patients tend to sign them without reading them in their entirety. However, certain issues need to be pointed out to them. The investigator needs to disclose the type of study, the names of the investigators and sponsors, the goal of the trial, what the patient must do, how long their participation will take, what burden it will place upon them, and any risk of harm that might arise.

Consent forms are frequently grossly inflated with regard to the description of potential side effects, and written in a language that does not appear to reflect an intention to communicate effectively with the patients. Whilst the risk of side effects and dangerous toxicities must be disclosed, it is reasonable to expect that treatments in use in standard care should only need to be disclosed in a manner consistent with routine care.

The type of toxicity that should be brought to the patient's attention in information related to a study is the additional toxicity conferred by a new treatment, or by its combination with existing treatments. Moreover, highlighting risks, such as the risk of secondary malignancy due to radiation exposure during imaging, is most certainly futile in a cancer patient who has a limited life expectancy. However, these items are part of consent forms, and often their disclosure is required by law or according to guidelines.

#### Remuneration

At present, there is a debate as to whether or not it is legitimate to offer payments to patients for trial participation, and what, if any, the appropriate amount of money should be. This is not an easy question to answer, as it appears reasonable to provide a person with compensation for loss of earnings to participate in a study on the basis that if this was not available, they could not participate, and this in itself would be unjust. However, defining what this amount should be is very difficult, as trial participants span the socio-economic spectrum. Equally, a fixed amount might be insufficient for some and yet an inducement to participate for others. Investigators should consider this as part of the recruitment strategy, as limiting access to specific parts of the community might lead to bias in the reported outcomes if certain sectors are excluded.

#### Take home message

Patient consent must be voluntary, informed, and based on mutual understanding. The type of study, the names of the investigators and sponsors, the goal of the trial and its risks are the main aspects that should be disclosed to the patient. Remuneration is currently under debate, to ensure that it is not viewed as an inducement.

## Role and responsibilities of the Principal Investigator

Good Clinical Practice sets out clear guidance for the responsibilities of a

TABLE 2

**General responsibilities of a PI**

Ensuring that an investigation is conducted according to ICH guidelines and GCP, as well as in accordance with other relevant ethical and legal frameworks

Signing an investigator statement, the study protocol, the IRB requirements, and all of the applicable federal, state, and institutional regulations

Monitoring all drugs/ agents/ devices under investigation

Protecting the rights, safety, and welfare of the patients under the PI's care

Maintaining a list of research team members to whom trial-related duties have been delegated\*

Keeping research team members well-informed about the trial at all times\*

Permitting monitoring, auditing, and inspection by sponsors and regulatory authorities\*

ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

IRB: Institutional Review Board

\* These responsibilities often apply to the institution rather than the PI

Principal Investigator (PI) who is responsible for a particular study at an individual trial site [2]. PIs are mandatory from both a regulatory point of view, and the point of view of the sponsor. If a sponsor is missing, as for investigator-initiated trials, the PI is the sponsor-investigator, or their institution may take on this role. The chief or lead investigator (CI) is usually the overall study lead, and it is particularly important to define their role in multicenter studies. However, the PI at the site bears a great deal of the responsibility, as identified by GCP.

**Qualifications and duties of a PI**

The PI should be qualified for their function, according to their education, training, and experience. Responsibilities of a PI include ensuring they have adequate provision for insurance and indemnity, for recruiting patients and ensuring their safety, and for the appropriate data collection (**Table 2**). The PI is obliged to establish structures for optimal trial conduct (e.g., trial clinics, fellows, study teams) and for holding regular meetings and updates with the research team. In practice, many functions will be performed by the study coordinator, although delegation is permissible as long as this is clearly defined and recorded. The PI must read the protocol, and however, and confirm that they have done so by signing of the document. They are also legally responsible for any harm that comes to a patient if the protocol is not followed.

Moreover, the PI is responsible for patient screening and the selection of suitable patients. They must obtain the informed consent of each person to

whom the drug/ agent/ device is distributed. Appropriate data collection is imperative to ensure the success of a trial. Furthermore, the PI has the legal responsibility for training the relevant staff, and for the consequences of any mistakes the study coordinator might make.

In principle, the PI's duty is primarily to the patient [3]. The patient's welfare must always take precedence over the interests of science and society, and ethical considerations must take priority over laws and regulations.

**Control of investigational drug/ agent/ device**

Responsibility for the investigational product and accountability at the trial site rests with the PI, but can be delegated to a pharmacist or another appropriate individual under the PI's supervision, in terms of the drug storage, and the keeping of accurate records and an inventory. The PI should distribute the drug/ agent/ device only to those under their personal supervision or under the supervision of a sub-investigator who is responsible to the PI. The drug or device must not be supplied to any person who is not authorized by the PI to receive it.

**Investigator record keeping**

Record keeping is required with regard to the Case Report Form (CRF) and Case Histories, as well as the disposition of the drug/ agent/ device. The CRF is a printed or electronic document that is designed to record protocol-required information on each subject. Here, the PI should ensure the accuracy, completeness, and timeliness of the data.

These data must be consistent and verifiable with the source documents. Also, it is the PI's duty to correct, as needed, the data in the CRF by striking out and initialing. 'White-Out' should not be used, and words should not be scribbled out.

For Case Histories, it is the PI's responsibility to prepare and maintain these adequately and accurately. Case Histories should record all of the observations and other data pertinent to a study for each patient to whom the active treatment was distributed to or who was used as a control in the protocol. Case Histories comprise the CRF, supporting data, the signed consent forms, the patient's medical records, progress notes, hospital charts, and the nurse's notes. They should document that informed consent was obtained prior to the patient's participation.

For the disposition of the drug/ agent/ device, the PI is obliged to maintain adequate records (e.g., dates, quantities, subject use, shipping, storage, return/ destruction). Furthermore, the PI is responsible for record retention.

**Reporting**

The reporting duties of the PI include progress reports, safety reports, financial disclosure reports, and the final report (**Table 3**). In addition, the Ethics Committee needs to be kept informed of anything that might reflect on a continued favorable ethical view of a study. Any new information that becomes available during the course of a trial and that is relevant to the continued safe conduct of the trial or a change in the protocol must be forwarded to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). Updated consent forms are necessary if the new information is relevant to patient participation, and these must be approved by the IRB/IEC prior to being given to the patients to confirm their willingness to remain in the study.

For trials conducted in the USA, sponsor-investigators are required to submit annual reports on the progress of the clinical investigation to the FDA, and also to report adverse effects that are both serious and unexpected, and/or deaths, to the FDA. Adverse events are defined as any untoward medical occurrence in a patient participating in



TABLE 3

**Reporting duties of the PI**

<b>Progress Reports</b>	
	Sending reports to the sponsor, as required by the protocol
	Sponsor-investigators are required to submit annual reports to the FDA on the progress of the clinical investigation
<b>Safety Reports</b>	
	Promptly report to the sponsor any adverse events that might reasonably be regarded as caused by, or probably caused by, the drug/ agent/ device
	Sponsor-investigators are required to report adverse events that are both serious and unexpected, and/or deaths, directly to the FDA
<b>Financial Disclosure Reports</b>	
	Provide the sponsor with sufficient accurate and current financial information to allow for accurate certification/ disclosure, as required
<b>Final Report</b>	
	Provide the sponsor/ FDA (for sponsor-investigators) with an adequate report shortly after completion of the investigation

a study, even though they might not necessarily have a causal relationship with the study treatment. The definition of serious adverse events extends to any untoward medical occurrence that meets one or more of a number of criteria, including a fatal outcome, a life-threatening situation, or the necessity for inpatient hospitalization.

The final report provides the sponsor or the FDA (for sponsor-investigators) with an adequate report shortly after the completion of the investigation.

**Conflicts of interest**

All investigators will have competing interests that can be described as finan-

cial, academic, or personal in nature. **Table 4** lists types of conflicts and means to avoid them. Special considerations apply to the situation of the clinician-investigator whose dual allegiance might result in a conflict between their duty to recruit patients and their duty to complete a study; i. e., meeting their duty to offer the best advice to the individual patient and their contractual obligations [4]. All options should be discussed with the patient, and the informed consent documentation must include disclosure of any competing interests that are real or can be perceived by potential participants.

**Take home message**

The PI is in control of the trial at a specific site. The PI is responsible for training the staff, recruiting the patients, ensuring patient safety, control of the investigational drug, and appropriate data collection, record keeping, and reporting. If there is no direct sponsor, the PI is the sponsor-investigator. The patient's welfare must always take precedence over the interests of science and society, and over laws and regulations.

TABLE 4

**Types of conflicts of interest and how to avoid them**

<b>Types of conflict</b>	<b>How to avoid clinician conflict</b>
Placebo-controlled trials where evidence has shifted practice such that use of a placebo can be questioned	The informed consent process should include unbiased discussions of all options  - There should be genuine clinical equipoise around the clinical question
Variations in accepted practice for use of standard therapy in control arms	Variations in practice can be accounted for in the trial protocol  - "Clinicians' choice" reference therapy, stratification by centers, regions, or countries
"Window of opportunity" trials	Open-label drug access upon disease progression in the placebo arm, or mandatory crossover

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This image shows a full page of blank, lined paper. It features approximately 20 evenly spaced horizontal grey lines across its entire width, providing a guide for handwriting or typing. The background is a clean, solid white color.

