PRECISION MEDICINE AND THE N-OF-1 CLINICAL TRIAL CONCEPT

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List of Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AMA	„Evidence-Based Medicine“ (EBM) Working Group of the „American Medical Association“ (AMA)
API	Application Programming Interfaces
AR	Annual Reports
ATMP	Advanced Therapy Medicinal Product
BPI	Bundesverband der Pharmazeutischen Industrie
CC	Cervical Cancer
CCHMC	Cincinnati Children’s Hospital and Medical Center
CE	Conformité Européenne
CDx	Companion Diagnostics
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
COMP	Committee for Orphan Medicinal Products
COPD	Chronic Obstructive Pulmonary Disease
CP	Centralized Procedure
CRISPR/Cas9	Clustered Regularly Interspaced Short Palindromic Repeats/ CRISPR-associated protein-9 nuclease
CRO	Contract Research Organization
CSA	Coordination and Support Action
CSP	Clinical Study Protocol
CTA	Clinical Trial Applications
CTD	Common Technical Document
CTS	Common Technical Specifications
C3N	Collaborative Chronic Care Network
DCP	Decentralized Procedure
DGRA	Deutsche Gesellschaft für Regulatory Affairs
DIA	Drug Information Association
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
EBM	Evidence-Based Medicine
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Area
e.g.	example given
HER	Electronic Health Record
ELSI	Ethical, Legal, and Social Issues
EMR	Electronic Medical Record
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
ER	Estrogen Receptor
ERA	Environmental Risk Assessment
EU	European Union
EU-MSs	European Union Member States
EU RING	European Union Regulatory Intelligence Network Group
EWG	Extrapolation Working Group

FDA	Food and Drug Administration
FP7	Seventh Framework Program
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
H0	Null Hypothesis
HA	Alternative Hypothesis
HBGRD	Human Biobanks and Genetic Research Databases
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICD	International Classification of Disease
IC PerMed	International Consortium for Personalized Medicine
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICT	Information and Communications Technology
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
IND	Investigational New Drug
iPOP	integrative Personal Omics Profile
IRB	Institutional Review Board
IT	Information Technology
IVD	In Vitro Diagnostic
JRC	Joint Research Center
KDI	Knowledge and Data Integration
LEEM	Les Entreprises du Médicament
MAA	Marketing Authorization Application
MD	Medical Device
MDCG	Medical Device Coordination Group
MoA	Mode of Action
MP	Medicinal Product
MRCT	Multi Regional Clinical Trials
MRP	Mutual Recognition Procedure
NB	Notified Bodies
NCA	National Competent Authority
NCE	New Chemical Entity
NCI	National Cancer Institute
NIH	National Institutes of Health
NP	National Procedure
ONC	Office of the National Coordinator for Health Information Technology
OECD	Organization for Economic Co-Operation and Development
OD	Orphan Disease
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PDCO	Pediatric Committee
PerMed	Personalized Medicine
PHR	Personal Health Records
PK	Pharmacokinetics
PM	Personalized Medicine

PR	Progesterone Receptor
PRO	Patient-Reported Outcomes
RA	Regulating Authority
RCT	Randomized Controlled Trial
RI	Regulatory Intelligence
RMS	Reporting Member State
RNA	Ribonucleic Acid
SAR	Serious Adverse Reaction
SAWP	Scientific Advice Working Party
σ	Standard Deviation
SME	Small to Medium sized Enterprise
SMS	Short Message Service
SRIA	Strategic Research and Innovation Agenda
SUSAR	Suspected Unexpected Serious Adverse Reaction
3-D	Three-Dimensional
TCGA	The Cancer Genome Atlas
USA	United States of America
US$	United States Dollar
Var	Variance
VFA	Verband Forschender Arneimittelhersteller
WHO	World Health Organization

Part I: The Current Status of Biomedical Research, Precision Medicine Initiatives and Clinical Trial Concepts

1. Introduction

The development of new medicinal products is associated with significant risks, and in particular, late stage failures are associated with a heavy financial impact for pharmaceutical companies. In a recent study published in November 2014, the authors calculated, that the estimated average pre-tax industry cost per new prescription drug approval increased from US$ 1044 million for the decade 1990-2000 to US$ 2558 million for the decade 2000-2010 [1].

The most common case for late stage attrition relates to failure in demonstrating sufficient efficacy in pivotal clinical trials. Stratification of the drug development process by identifying subpopulations of patients that are expected to respond has been successfully implemented only for oncolytic drugs based on genetic markers. A systematic application of efficacy pharmacogenetics has not been adopted in the pharmaceutical industry, primarily due to the lack of clinically relevant biomarkers. The early identification of such predictors and their integration into subsequent clinical development in conjunction with patient specific factors is expected to provide comprehensive data sets to understand mechanistic interactions and inter-individual variabilities. Providing evidence to „Regulating Authorities“ (RAs) and „Health Technology Assessment“ (HTA) bodies why individual patients did or did not respond to a drug could result in a higher success rate of clinical efficacy trials [2].

The scientific knowledge on molecular mechanisms underlying human diseases as well as advances in molecular profiling and diagnostics of individual patients is continuously expanding. Consequently, the paradigm to focus on average responses by monitoring a limited number of clinical parameters in large cohorts during clinical trials and pharmacovigilance activities after marketing authorization is increasingly challenged. Scientists discuss a shift towards data collection and management of multiple clinical parameters in individual patients during treatment and non-treatment periods, referred to as „integrative Personal Omics Profile“ (iPOP) [3].

It is suggested, that the application of the personalized medicine approach requires “*studies that focus on a single person – known as N-of-1 trials*”. Nevertheless, ”*formalizing and scaling up the N-of-1 approach will”…“require a cultural shift on many levels – in regulatory agencies, in pharmaceutical companies and, most of all, in the clinic*” [4].

The first part of this Master Thesis provides an introduction to the area of research, (Chapter 1), describes recent advances in biomedical research (Chapter 2), summarizes current initiatives on precision/personalized medicine imposed by the governmental administrations in the „European Union“ (EU) and the „United States of America“ (USA) (Chapter 3) and provides an overview on different clinical trial concepts including latest changes of trial designs to reflect precision

medicine approaches (Chapter 4). The second part of the thesis focusses on the identification of organizational, technical and scientific requirements for clinical development programs implementing precision medicine N-of-1 Clinical Trials (Chapter 5), discusses new ethical considerations and regulatory aspects including suggestions to modify and further clarify existing regulatory guidelines (Chapter 6) and closes with concluding remarks and thoughts on precision medicine approaches as part of future health care solutions (Chapter 7).

2. Advances in Biomedical Research

2.1. The „OMICS“ Era

The scientific project to sequence the 3 billion DNA letters of the human genome is considered the starting point of the genomic era [5], [6]. Since then, genomic technologies have significantly advanced with an increasing impact on biomedical research and drug development e.g. reflected by the „.The 1000 Genomes Project Consortium“ that published an integrated map of genetic variation from 1,092 human genomes and a global reference database for human genetic variations [7], [8].

In 2015 the „International Cancer Genome Consortium“ project to sequence 10.000 tumor genomes was accomplished and „The Cancer Genome Atlas (TCGA)“ was presented to the public [9]. Genomic analysis has proven to be a powerful tool to discover hereditary factors of disease, but a distinct phenotype, e.g. state of health or disease is determined by the interplay of genetic and environmental factors. Interestingly, the end of the cancer-genome project triggered a debate among geneticists whether the focus of cancer research should shift from sequencing genomes to analyzing function [10].

Over the last two decades, several genome editing techniques were invented to facilitate functional genomic approaches. However, only recently, the application of the CRISPR/Cas9 technology seems to allow for precise modifications of the human cellular genome to enable disease modelling [11], [12], functional genomics [13], and even corrective somatic gene therapy [14], [15]. In fact, recent publications demonstrate, that the CRISPR/Cas9 technology represents an important breakthrough in human genomic engineering by combining highly efficient „on-target“ activity with a low probability of introducing „off-target“ mutations. Modified human stem cells are currently evaluated in clinical trials e.g. for regenerative medicine or HIV treatment to evaluate the risk-benefit-ratio for patients [16], [17].

In contrast to somatic gene therapy approaches, the therapeutic germline modification of genes in humans remains challenging, both for technical and ethical reasons. Addressing the non-genetic environmental and/or lifestyle aspects affecting human health will remain the key factors to translate scientific knowledge into therapeutic improvements for patients. For complex diseases involving multiple genes and biological pathways, such as cardiovascular disease, metabolic syndrome, diabetes, neurological syndromes and various cancer types, non-genetic treatment options will remain the predominant therapeutic concept [18], [19], [20].

The necessity to understand mechanistic processes and signal transduction pathways on the cellular, tissue and organ level supported the development of novel technologies for large-scale analysis of molecular markers like transcripts, proteins and metabolites. Table 1 below displays the most frequently used high throughput techniques applied in biomedical research and development.

Biotechnologies	Experimental data	Representative databases
DNA-seq, NGS	DNA sequences, exome sequences, genomes, genes	GenBank109, DDBJ110, Ensembl111
Microarray, RNA-seq	Gene expression levels, microRNA levels, transcripts	GEO112, Expression Atlas113
MS, iTRAQ	Protein concentration, phosphorylations	GPMdb, PRIDE, Human Protein Atlas22
C-MS, GC-MS, NMR	Metabolite levels	HMDB, GMD
ChIP-chip, ChIP-seq	Protein-DNA interactions, transcript factor binding sites	GEO112, TRANSFAC, JASPAR, ENCODE, modENCODE
CLIP-seq, PAR-CLIP, iCLIP	MicroRNA-mRNA regulations	StarBase114, miRTarBase
Y2H, AP/MS, MaMTH, maPPIT	Protein-protein interactions	HPRD115, BioGRID116, DIP, IntAct, and MINT, CCSB interactome database
Protein microarray	Kinase–substrate interactions	RegPhos, PhosphoPOINT
SGA, E-MAP, RNAi	Genetic interactions	HPRD115, BioGRID116
SNP genotyping array	GWAS loci, eQTL, aberrant SNPs	GWAS Catalog, GWASdb, GTEx, dbGAP, dbSNP HGMD
LUMIER, data integration	Signaling pathways, metabolic pathways, molecular signatures	KEGG, ConsensusPathDB, BioCart, Pathway Commons, MSigDB, Reactome, BiGG

Table 1: A list of high-throughput technologies and the data they generated, with representative databases, depicted from Wang et al. [21]

Combining the information obtained from genomic sequencing and molecular profiling of biopsies is considered crucial to understand the onset, progression and prevalence of disease states and therefore to predict, diagnose and treat human diseases. Snyder et al. developed a model named „integrated Personalized Omics Profiling“ (iPOP) to integrate the medical history, environmental factors, microbiological analysis of the gut and molecular data on DNA-, RNA-, protein- and metabolic-level obtained from an individual‘s biopsies to analyze the health/disease status to identify optimal personalized treatment options and to monitor treatment effects [22], [23].

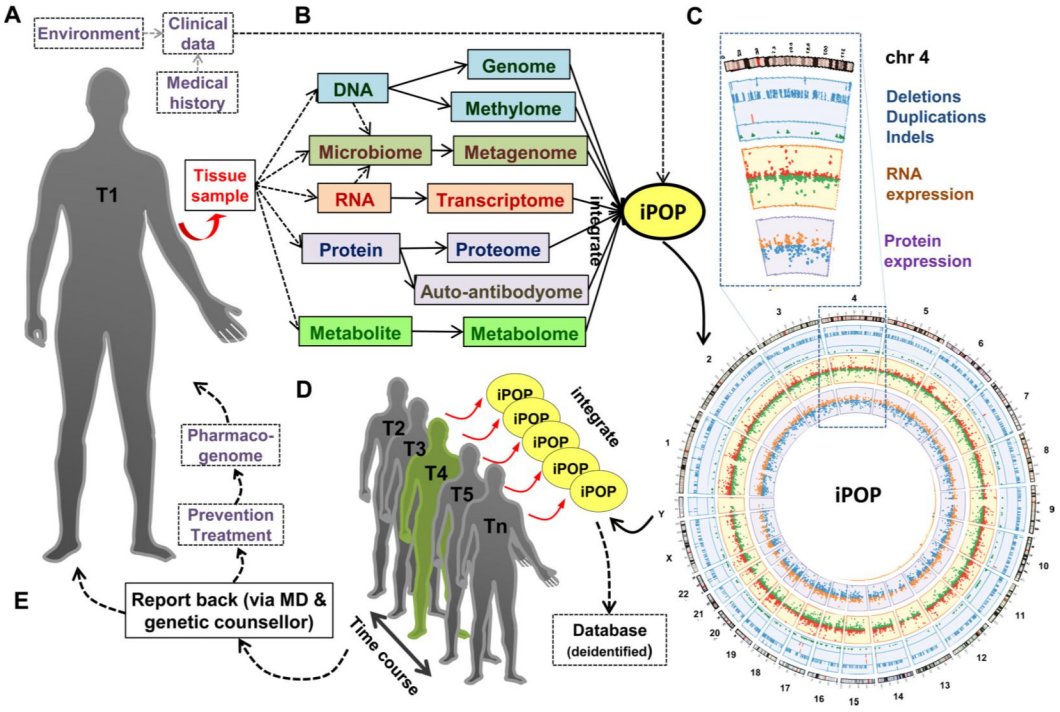

Fig. 1: Schematic representation of the implementation of iPOP for personalized medicine, depicted from Li-Pook-Than J. and Snyder M. [23]

(A) Participant tissue sample e.g. „Peripheral Blood Mononuclear Cells“ (PBMCs) is collected, while environment (incl. diet, exercise, etc.), medical history and clinical data are recorded. T1 is the first time point.
(B) Selected omic analysis involved in a sample iPOP study (Chen et al., 2012).
(C) Sample Circos plot (Krzywinski et al., 2009) of DNA (outer ring), RNA (middle ring) and protein (inner ring) data matching to chromosomes.
(D) iPOP performed and integrated at multiple time points: T2, T3, T4 (viral-infected), T5 up to Tn states, including disease-state(s). Grey and green forms represent relative-healthy individual and a disease-state, respectively.
(E) Report data back to genetic counsellor and medical practitioner with better informed choices for prevention and/or treatment (matched with pharmacogenetic data), if needed.

2.2. Identification of Biomarkers and Correlation with Diseases and Disease Progression

The „NCI Dictionary of Cancer Terms“ defines a biomarker as „a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition, also called molecular marker and signature molecule“ [24]. With other words, a biomarker is defined as a clinical parameter, which is objectively measured and evaluated as an indicator of a phenotype e.g. normal biologic processes, disease processes, or biological responses to a therapeutic intervention and frequently utilized to reduce diagnostic uncertainty and guide clinical care.

„Genetic information obtained by genomic sequencing is likely to be of limited value to the individual, as the number of loci that provide useful predictive information is quite small (probably less than 200)."...and..."*the ability to accurately correlate all bases with precise phenotypes is likely to be powerful only if a common set of phenotypes are scored*" [25]. Therefore, Snyder et al. suggest that a panel of „General", „Behavioral & Cognitive" and „Molecular" data sets is most useful when obtained from each individual to identify biomarkers that correlate with disease and disease progression as outlined in Table 2 below [25].

General	Anatomical height, body mass, blood pressure, morphometric medical history (disease conditions, medical treatment, medication, etc. asthma, infections, cancer, other diseases)
Behavioural & Cognitive	Anxiety, depression, hyperactivity, sleep, cognitive attributes (learning and memory, 'intelligence')
*Molecular**	RNA expression, proteomics (mass spectrometry, antibody profiling), metabolomics, microbiome metagenomics

*Types of samples to analyze: saliva, plasma, serum, urine, breath, skin (stem cells), feces (microbiology).

Table 2: Examples of data types to consider for collection [25]

Molecular markers like transcripts, proteins and metabolites display dynamic changes over disease states and allow for more comprehensive monitoring of disease progression. The activation of signaling pathways can be deduced by aligning the genome sequence with transcript- and protein-expression and post-translational modification data. Moreover, the molecular information obtained could be used to expand medical diagnostics. It is expected that the analysis of hundreds or even thousands of transcripts, proteins or metabolites will improve early and accurate diagnostics compared to the few parameters currently monitored as part of the clinical chemistry standard program.

Phenotypic data is only useful if it is collected based on common methods and standards and samples, and measurements are obtained using the same methodological approach and robust analytical procedures. The minimum requirement would include a description of the method used for sample preparation and analysis and a description of the classification system used to record the medical and psychiatric histories and physical examinations for each individual. It is evident that the collection, electronic storage and retrieval of sensitive personal data will create controversial discussions, but a valuable genotype–phenotype correlation will require a comprehensive phenotype database covering all relevant clinical parameters including biomarkers.

In 2005 the FDA issued a draft paper „on how to prospectively co-develop a drug or biological therapy (drugs) and device test in a scientifically robust and efficient way“ [26]. The term „Companion Diagnostics“ (CDx) refers to a test used as a companion to a therapeutic drug in order to determine its applicability to a specific patient or group of patients. The latter allows the early identification of meaningful clinical biomarkers and the development of tests to reveal the efficacy and/or safety of a specific drug for a targeted patient group as part of a drug development program. During the last decade, ICH regulatory authorities issued guidance documents and proposed new regulations reflecting the co-development with a drug that requires an exclusive diagnostic test or medical device to predict efficacy or adverse drug reactions [27], [28], [29], [30], [31].

2.3. Paradigm Shift from Clinical to Molecular Classification of Diseases

Throughout medical history the classification of diseases was crucial for diagnosis and the decision making process on the most suitable treatment. Historically, the nomenclature of diseases was primarily based on their location in the human body and further categorized according to pathological criteria exemplified for the classification of cancer types. To date, in the USA, the „National Cancer Institute“ (NCI) has defined approx. 200 types of cancer categorized primarily according to organ-specificity including subgroups reflecting the patient age or the cell types affected [32].

As an example, „Breast Cancer“ is defined as a tumor originating from mammary tissue further specified according to criteria such as patient age, cell type, historical grades and molecular markers, e.g. the expression of hormonal receptors. The changes in breast cancer classification based on the evolving biomedical knowledge during the genomic era reflect the current taxonomic challenges. Traditionally breast tumor biopsies were analyzed via immunohistochemistry for the presence or absence of hormone receptors, e.g. the estrogen receptor (ER), the progesterone receptor (PR), or the human epidermal growth factor receptor 2 (HER2) to identify patients for selected hormonal or molecularly targeted therapies [33]. The genomic analysis of several thousand malignant breast tumor samples expanded the classification portfolio to ten different molecular subtypes [34]. Furthermore, the application of multiple –OMICS platforms revealed complex genetic similarities across different types of cancers [35] and provided independent and clinically relevant prognostic information above and beyond tumor stage and primary tissue-of-origin of 12 cancer types. As discussed by Hoadley et al., 2014 „*one in ten cancer patients would be classified differently by this new molecular taxonomy versus the current tissue-of-origin tumor classification system*“ [36].

A continuously evolving and more detailed classification system is beneficial to reflect the biological diversity and could improve the diagnosis of patient-specific disease mechanisms. In fact, the concept of precision medicine relies on exact classification of a patient‘s disease, e.g. tumor subtype, to select and apply the most suitable treatment option. This is especially relevant as tumors display a spatio-temporal heterogeneity. Intratumor spatial variability depends mainly on the number of clonal populations and could be addressed by sequencing

multiple regions, whereas the tumor development over time is reflected in a limited way, as biopsies are usually taken at a single time point. This histological analysis in combination with molecular profiling of tumor biopsies provides diagnostic means to apply targeted therapies in precision medicine cancer therapies. Nevertheless, it needs to be demonstrated, that a new molecular classification system could replace the classical taxonomic system in tumor pathology or that it could be applied to other disease areas e.g. cardiovascular, metabolic or mental syndromes. If so, this would allow the comparison of molecular data across clinical trials, which ultimately results in clinical benefits for patients.

2.4. Summary: Advances in Biomedical Research

"Reverse genetics approaches" were successfully applied in biomedical research to uncover genetic polymorphisms in human individuals and their correlation with disease phenotypes. However, only the development of multiple OMICs technologies and their application in a high-throughput manner during the last decade allowed understanding the mechanistic aspects and signaling transduction pathways on cellular- tissue- and organ level. Furthermore, the identification of biomarkers such as transcripts, proteins and, metabolites, and their changes during disease and disease progression provided the basis for a new classification system based on molecular characteristics. As an example, clinical oncologists combine traditional procedures such as histopathological analysis with latest technologies to assess the molecular signatures of individual tumors. The combined data sets are used to more accurately describe and reclassify cancer types based on molecular findings, which in turn provide the basis for targeted therapeutic strategies.

3. The Precision / Personalized Medicine Initiatives

The terms „Precision Medicine" and „Personalized Medicine" are frequently used synonymously. *„Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. This approach will allow to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people*" [37]. The term „Precision Medicine" is prominently used to describe effective therapeutic approaches for patients based on genetic-, environmental-, and lifestyle factors and to avoid misinterpretation, that these treatments and preventions are being developed uniquely for each individual. Since many years, the concept of „Precision Medicine" is part of the medical therapy in transplantation- and transfusion-medicine by matching donors and recipients based on genetic factors to minimize the risk of adverse events. Nevertheless, the relevance in daily healthcare is still limited in terms of providing the most suitable drug with the optimal dose regimen to individual patients as part of the first therapeutic treatment by applying molecular biomarker tests.

3.1. The European Union (EU)

In the EU advances in Personalized/Precision Medicine are supported by multiple initiatives and programs. The „Innovative Medicines Initiative“ (IMI), a public/private partnership between the EU, represented by the „European Commission“ (EC) and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), provides financial support to major research projects. The program aims to accelerate the development of next-generation vaccines, medicines, and treatments focusing on new and approved diagnostic markers for immunological, respiratory, neurological and neurodegenerative diseases. The initiative's second phase, named IMI 2, started in 2014 with a total budget of €3.3 billion for the period 2014 – 2024 with

- €1.638 billion provided by Horizon 2020, the EU's framework program for research and innovation;
- €1.425 billion committed to the program by EFPIA companies;
- up to €213 million that can be committed by other life science industries or organizations that decide to contribute to IMI 2 as members or Associated Partners in individual projects [38].

In the EU, the term Personalized Medicine „*refers to a medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention*“ [39].

PerMed, an EU funded „Coordination and Support Action“ (CSA) representing key decision makers in research, research-policy, -industry, -healthcare and patient organizations [40], generated a „Strategic Research and Innovation Agenda“ (SRIA) with general recommendations and research activities to support the further implementation of „Personalized Medicine“ (PM) in Europe (see Figure 2 below). While PM approaches for diagnosis and treatment of cancer and orphan diseases are already being implemented, other areas such as the treatment of cardiovascular diseases, metabolic syndrome, allergies, airways diseases and mental disorders are still awaiting concepts to be developed. The SRIA defined five major challenges to advance PM and suggested 35 recommendations to address these challenges, whereby nine high priority recommendations are expected to provide the highest impact to facilitate the introduction in the areas of highest medical need for the benefit of patients, citizens and health care systems (for further information see Annex A).

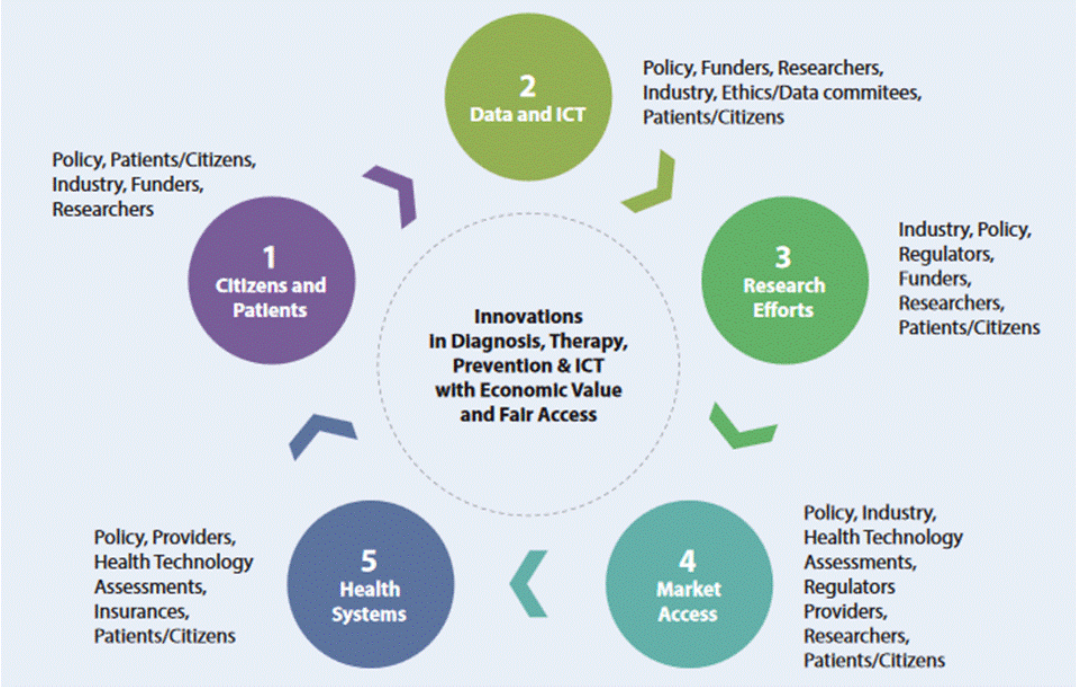

Figure 2. Circle of Challenges with important enablers and stakeholders. The overall aim of PM research and implementation is in the center of the circle [40].
Challenge 1: Developing Awareness and Empowerment
Challenge 2: Integrating Big Data and ICT Solutions
Challenge 3: Translating Basic to Clinical Research and Beyond
Challenge 4: Bringing Innovation to the Market
Challenge 5: Shaping Sustainable Healthcare

The Personalized Medicine Conference held on 1-2 June 2016 in Brussels and organized by the European Commission [41] published actionable items to address these five challenges and introduced a new forum among health research funding and policy making organizations named the „International Consortium for Personalized Medicine“ (IC PerMed). The development effort on the five challenges is led by „Challenge Facilitators“ nominated by the IC PerMed member organizations, who will oversee the implementation of the roadmap and function as primary contact points for stakeholders. The number in brackets () below refer to the 35 recommendations listed in Annex A [40].

„Challenge 1: Developing Awareness and Empowerment

With the advent of PM, the role of caregivers and patients will evolve. Successful implementation of PM will be achieved only if all stakeholders, including patients and healthcare professionals, are empowered and develop the required awareness about PM. The crucial first step is to provide the best available evidence that supports the clinical and personal utility of PM, as well as its economic value to health systems, and to enable better understanding of how the changes brought by PM will impact public health for the benefit of individual citizens and society (recommendations 1,4). Models that enable sharing, ownership and the development of a sense

of responsibility towards personal health data, as well as the improvement of PM health literacy, will need to be generated along with suitable common principles, appropriate policy and regulatory frameworks (2,5,7). Public engagement in PM can be increased by enabling citizens to become actively involved in all phases of research and development ('citizen science'), and the introduction of mobile health applications will facilitate data generation about the safety and effectiveness of interventions (3,6).

Challenge 2: Integrating Big Data and ICT Solutions

The development of PM will rely heavily on integrated 'big data' analytics and ICT solutions to generate the required knowledge and infrastructure to support the new approaches. Technologies for data capture and management and development of high quality databases will be instrumental, but there will also be a requirement for strategies to make sense of this big data for known and future purposes (8,9,10). Translational research infrastructures and data harmonization of structured, semi-structured and unstructured data will be a central component of such strategies and should lead to new analytical methods and modelling approaches as well as innovative decision support tools such as in silico simulations to support physicians' decisions (11,12,13). To integrate all these aspects, further European big data and 'big science' frameworks need to be created and supported by suitable legislation (14).

Challenge 3: Translating Basic to Clinical Research and Beyond

In order for PM to reach its anticipated impact on human health and wellbeing, translation of discoveries and communication across the continuum of research are required. This starts with the integration of all 'omics' data to generate and implement meaningful interventions. Such processes should be supported by re-classifying diseases at the molecular level and by developing preclinical models to validate hypotheses resulting from molecular analyses (15,16,21). A Europe-wide process to evaluate and validate biomarkers, together with longitudinal and in-depth studies to further characterize diseases and their progression would support on-going efforts towards this integration and re-classification (18,19). The development of new clinical trial designs that are adapted to these new approaches and the integration of preclinical testing with innovative clinical trials may further improve the effectiveness of interventions (20). Collaborative pre-competitive and trans-disciplinary research and cross-sector collaborations need to be promoted and supported by suitable funding mechanisms in order to truly bridge all steps of the PM research continuum (17,22).

Challenge 4 – Bringing Innovation to the Market

Bringing innovative PM solutions to the market presents a new set of challenges, including the issue of uncertainty. There will be opportunities to support the development of new risk-based approaches for the evaluation of PM in a context that encourages systematic early dialogue with all stakeholders, including regulators, funders and innovators, providing guidance for companies to enter the market for PM (23,26,28). As is the case for the research continuum, partnerships and innovation networks need to encourage cross-disciplinary and cross-border collaboration,

and these would benefit from a transparent 'open Innovation' approach (27). Finally, research on appropriate policy, regulatory and legal frameworks would ensure that the new challenges associated with PM are adequately addressed from these perspectives (25).

Challenge 5 – Shaping Sustainable Healthcare

PM needs to rely on a knowledgeable healthcare system that is able to adapt to these new approaches in a timely and socially acceptable way, and that enables the participation of all stakeholders to increase PM's effectiveness and efficiency. The starting point for this requirement is the development of training programs on PM for health professionals, and promoting the engagement and close collaboration of all stakeholders, including patients (31,33). Patients and the citizen will play an increasingly important role in adopting and controlling the use of data from electronic health records and in developing prospective surveillance and monitoring systems for personal health data (30,32). To ensure the effectiveness of the healthcare system, health economics research relating to PM needs to be supported. In addition a flexible framework for pricing and reimbursement equitable for all patients needs to be developed (29,34), leading to an overall healthcare financing strategy that covers all aspects of PM (35)."

3.2. The United States of America (USA)

On January 30th 2015 the federal government announced a publicly funded initiative to expand the application of precision medicine in the US healthcare system. The 2016 budget of $215 million provided to the „National Institutes of Health" (NIH), together with the „Food and Drug Administration" (FDA), and the „Office of the National Coordinator for Health Information Technology" (ONC) included key investments of

- *„$130 million to the NIH for development of a voluntary national research cohort of a million or more volunteers to advance the understanding of health and disease and set the foundation for a new way of performing research through engaged participants and open, responsible data sharing.*
- *$70 million to the National Cancer Institute (NCI), part of NIH, to scale up efforts to identify genomic drivers in cancer and apply that knowledge in the development of more effective approaches to cancer treatment.*
- *$10 million to FDA to acquire additional expertise and advance the development of high quality, curated databases to support the regulatory structure needed to advance innovation in precision medicine and protect public health.*
- *$5 million to ONC to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems."* [42].

The program defines both short-term and long-term goals to generate scientific evidence as a basis moving the concept of precision medicine into clinical practice [43].

Short Term goals:

The short-term goals involve expanding precision medicine in the area of cancer research and clinical development based on increased knowledge of the genetics and biology of various types of cancer. The „National Cancer Institute“ (NCI) will accelerate the design and execution of innovative clinical trials for targeted therapies by expanding genetically based clinical cancer trials and explore the of use of combination therapies. The establishment of a national “Cancer Knowledge Network” is expected to facilitate the generation and distribution of new information e.g. on mechanisms of drug resistance and guide treatment decisions.

Long Term Goals:

The long-term goals of the „Precision Medicine Initiative“ aim to expand the application of precision medicine to all areas of the health sector by creating a research cohort of comprising at least 1 million volunteers living in the USA. The participants are requested to provide genetic data, biological samples to analyze e.g. metabolites and the gut microflora, diet/lifestyle information and additional information related to their personal health status as part of their electronic health records. The aggregated data will be analyzed to improve the prediction of disease risks, understand the development of diseases, improve diagnosis and develop new treatment strategies. Furthermore, existing research and clinical networks will be leveraged by the development of interoperability standards and requirements to ensure secure data exchange with patients’ consent.

3.3. Summary: The Precision / Personalized Medicine Initiatives

The PM-initiatives in the EU and USA pioneer a new model for performing healthcare related medical science that emphasizes engaged participants, responsible data sharing, and privacy protection. Expert representatives from e.g. regulatory authorities, patient groups, bioethicists, civil society interest groups, and information technology specialists are involved to identify and address legal and technical aspects related to the privacy and security of data in the context of precision / personalized medicine. Moreover, the current regulatory environment will be reviewed to evaluate if changes are required to support the development of the new research and healthcare model.

4. The Evolution of Clinical Trial Concepts:

Scientific studies in biomedical research involving human beings are classified into interventional and non-interventional studies as depicted in the flow diagram in Figure 3 below. The most important type of interventional studies to assess the efficacy and safety of „Investigational Medicinal Products“ / „Investigational New Drugs“ (IMPs / INDs) is the “Randomized Controlled Trial” (RCT).

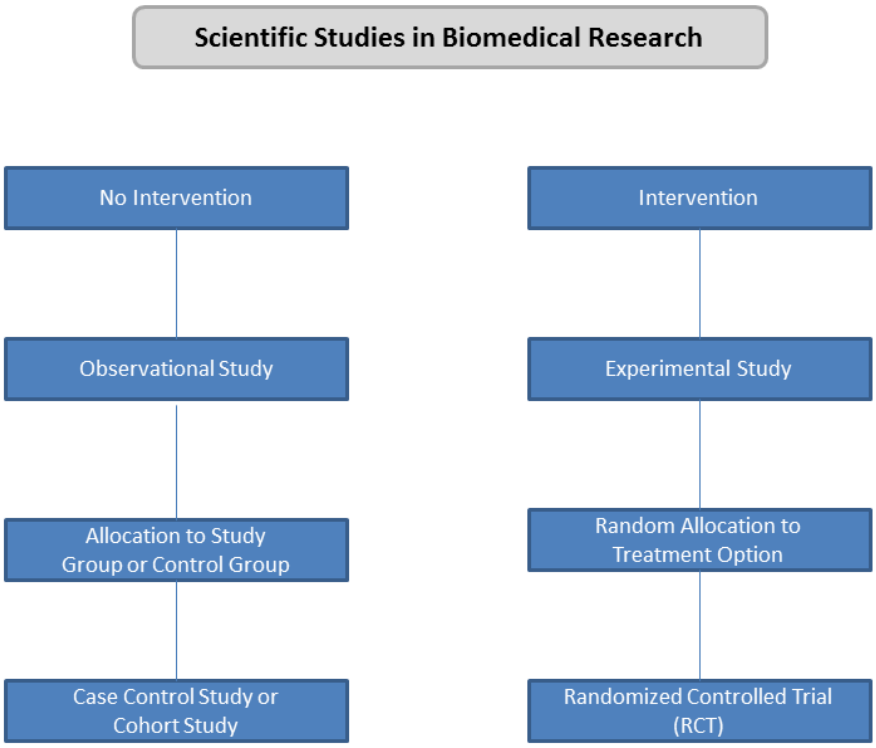

Figure 3. Overview: Comparison of interventional and non-interventional studies, depicted from Dr. Ritu Budania‘s presentation and modified [44]

RCTs are characterized by three features to ensure that each study group represents a random selection of the potential user population of the pharmaceutical product:

- Comparison of the product under investigation (verum) with a comparator as a control (placebo, standard of care, competitor product)
- Randomized distribution of study members (patients, volunteers) to the different arms of the study in a double-blinded way after being accepted for trial

- Prospective study design to test a hypothesis about a treatment (testing of new drugs, testing of known drugs in new indications, testing of new procedures) including pre-specified study protocol and data analysis plan

The RCT approach could be applied to studies for prevention, diagnosis and treatment of diseases and trials to analyze the quality of life.

In any clinical trial, a „Clinical Study Protocol“ (CSP) needs to be defined as a mandatory requirement. The CSP contains common elements such as inclusion and exclusion criteria for the study subjects, definition of subgroups for the study population and criteria for stratifying the study subjects, methods for recruitment, obtaining consent, randomization, allocation, statistical analysis and presentation of data sets. Moreover, the CSP typically includes a synopsis and a study schema and/or a flow chart of the study design, the identity of the IMP/IND and the control substance(s), and the identification of the clinical endpoints. Multiple study designs have been developed such as:

- Parallel- vs. Cross-Over-Design
- Superiority- vs. Non-Inferiority-Design
- Traditional- vs. Adaptive-Design
- Factorial- vs. Simple Parallel-Design
- Withdrawal-Design vs. Continuous Treatment Design

Advantages and disadvantages of the above mentioned concepts are described in detail in chapter two of „Clinical Trials, Study Design, Endpoints and Biomarkers, Drug Safety, and FDA and ICH Guidelines“ [45].

4.1. Legislation in the EU

The regulatory framework for pharmaceutical development intends to ensure that efficacious and safe high quality medicines are accessible to patients in need. Directive 2001/20/EC [46] outlines the approximation of the laws, regulations and administrative provisions of the Member States (MSs) relating to good clinical practice in the conduct of clinical trials on medicinal products for human use (Clinical Trials Directive). The Directive was issued in April 2001, implemented in May 2004 and translated into the national laws of the „European Union Member States“ (EU-MSs) with the intention of providing a harmonized framework for conducting clinical trials in the EU.

However, the disharmonized translation into national law and variable interpretation resulted in increased administrative effort, cost, delays for launch and risk of failure, especially when applying for a clinical trial involving several EU-MSs, as the authorization procedure by the „National Competent Authority“ (NCA) and the national „Ethics Committee“ are performed in each state individually. In order to overcome these limitations and to create an environment that is favorable for conducting clinical trials with the highest standards of patient safety for all

EU-MSs, the European Commission proposed a new regulation in 2012. In contrast to the current Directive 2001/20/EC, the new "Regulation" applies directly to all citizens of the European Union. Regulation (EC) 536/2014 was proposed by the European Commission on 17.07.2012, adopted by the European Parliament and European Council on 16.04.2014, published in the "Official Journal" on 27.05.2014 and came into force on 17.06.2014. The expected implementation date will be defined, when the necessary IT infrastructure (EU-Database, EU-Portal), to be provided by the European Medicines Agency (EMA), are in place and fully functional for at least 6 months [47].

The Clinical Trials Directive will be repealed on the day the Clinical Trials Regulation will be in force. It will, however, still apply three years from that day to i) clinical trials applications submitted before the date of repeal and ii) clinical trials applications submitted within one year after repeal if the sponsor opted for the old system. The most important changes in the new Clinical Trials Regulation are outlined below:

- Applicants/sponsors for clinical trials in Europe must submit a harmonized application via a single EU portal/database. The novel application dossier consists of 2 parts, which can be submitted in conjunction or in a sequential fashion in a two year time window. Part 1 contains common scientific documents and Part 2 contains national documents specific for the concerned member states. The regulation will also apply to all clinical trials conducted in non-EU countries, if the data will be used for a Marketing Authorization Application (MAA) in EU-MSs.
- One authorization procedure will be conducted by all Concerned Member States (CMS), whereby one CMS will function as Reporting Member State (RMS) ensuring one point of contact and single assessment outcome in max. 106 days (Advanced Therapy Trials 156 days max.).
- Implementation of the Co-Sponsorship Principle to the whole authorization process, which will facilitate clinical trial applications by Small to Medium sized Enterprises (SMEs) and academic researchers.
- Modified reporting schemes on patient recruitment and streamlined notification of suspected unexpected serious adverse reactions (SUSARS) via the EudraVigilance database at EMA are intended to improve patient safety.
- New rules are established to enhance transparency. All clinical trial information and results will be disclosed in a publicly accessible EU database one year after the trial end including a summary report in a comprehensive language unless confidentiality is justified. Sponsors will be subject to penalty fees in case of non-adherence to transparency requirements
- In addition, several key definitions like i) clinical trial, ii) clinical study, iii) start of a clinical study, iv) non-interventional study, v) substantial modification were clarified.

4.2. Data Requirements and Documentation:

The data sets and formal requirements to achieve marketing authorization approval are harmonized and published in the ICH M4 guideline referred to as "Common Technical Document" (CTD) [48] and the electronic counterpart eCTD [49]. Guidance on the structure and content on the clinical overview- and clinical summary-sections of module 2 and the study report of module 5 are provided in the ICH Topic M 4 E guideline [50] and the Revisions R1 [51] and R2 [52].

4.3. Novel Clinical Trial Concepts for Precision Medicine:

Precision medicine incorporates individual genetic variability, environmental- and lifestyle factors to prevent and treat diseases. The approach allows to more accurately predict treatment and prevention strategies for a particular disease in groups of patients displaying specific characteristics. In contrast to traditional treatment strategies that are developed for the „average" patient, precision medicine clinical trials are based on molecular profiling data (e.g. tumor profiles) and genomic markers (e.g. patient specific variations in disease related genes and Cytochrome P450 metabolizing enzymes) as acceptance criteria for clinical trial patient recruitment. These „Targeted Therapies" are expected to result in less severe adverse effects and include *„hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies, and toxin delivery molecules"* [53]. Traditionally, the site of tumor origin, in conjunction with histological analysis, was used as a basis for treatment decisions without knowing the underlying causative mutations (Figure 4).

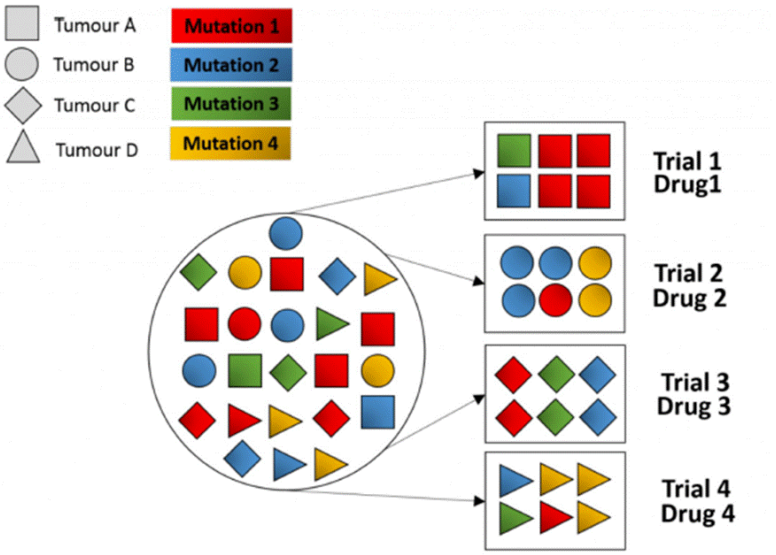

Figure 4: Traditional clinical trial based on tumor histology, depicted from BHD foundation, genetic sequencing approaches to cancer clinical trials, Posted on 2 Apr 2015 by Danielle Stevenson [54]

This classical approach has been superseded to include molecular tumor characteristics. Several innovative trial designs are currently applied for precision medicine clinical trials such as those described below.

- Basket Trials:

  In case of „Basket Trials“ the effect of one drug on a single mutation in a variety of tumor types is tested as part of the same clinical trial. These studies provide the potential to expand the number of patients who are eligible to receive a certain drug relative to other trials designs (Figure 5) [55], [56].

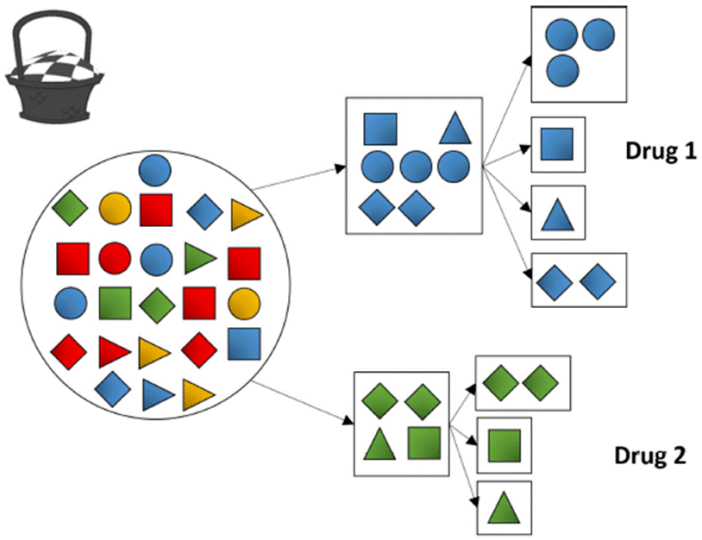

Figure 5: Basket clinical trial based on tumor genotype, depicted from BHD foundation, genetic sequencing approaches to cancer clinical trials, Posted on 2 Apr 2015 by Danielle Stevenson [54]

- Umbrella Trials:

  As opposed to „Basket Trials“, „Umbrella Trials“ have multiple treatment arms within a single trial. The patients are assigned to a particular treatment arm of the trial based on their type of cancer and the specific molecular profile of their tumor type (Figure 6) [57], [58].

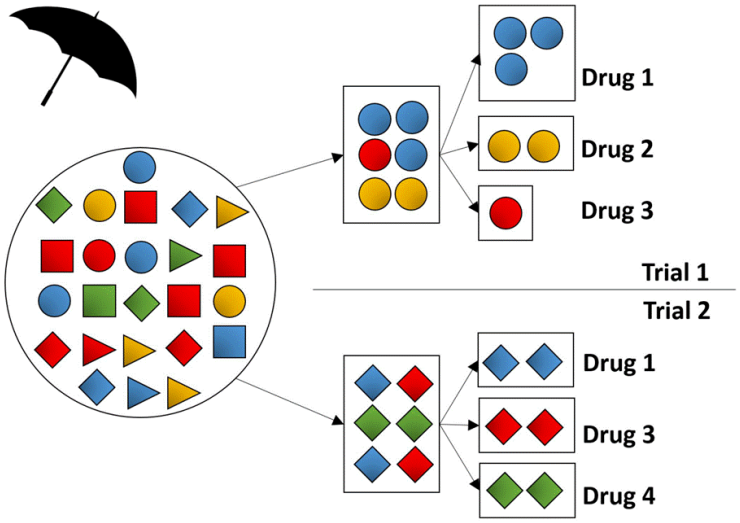

Figure 6: Umbrella clinical trial based on tumor histology and genotype, depicted from BHD foundation, genetic sequencing approaches to cancer clinical trials, Posted on 2 Apr 2015 by Danielle Stevenson [54]

Currently, biomarkers used to guide decisions for precision medicine treatment are predominantly DNA based, but additional tests of RNA, protein, and immune parameters are being developed and will be incorporated into clinical research. The comprehensive characterization of individual patients' molecular signature will display a pattern of potential therapeutic targets based on multiple detected markers. The specific data sets obtained from each individual will in turn restrict the number of patients that match the defined acceptance criteria (e.g. molecular markers) for a precision medicine clinical trial. The limited accessibility to patients resembles the situation of clinical research for rare diseases and requires administrative and scientific solutions to address the associated issues [59].

4.4. The N-of-1 Clinical Trial:

„*N-of-1 or single subject clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions*" [60], and are discussed to be the optimal strategy to identify and apply the optimal intervention for an individual patient. N-of-1 trials have a long tradition in medicine to generate treatment information when evidence from randomized controlled trials (RCTs) is not available or feasible. „Overall, N-of-1 study design maintains methodological safeguards provided by RCTs (blinding, randomization, controls) yet avoids many of the pitfalls of large trials, such as recruitment issues, prohibitive expense, and lack of external validity (i.e., applicability to patients not fitting stringent trial eligibility criteria)" [61]. Table 3 below summarizes strengths and limitations of single patient trials.

Feature	Description	Indication	Contraindication
Heterogeneity of treatment effects (HTE)	Treatment effect varies across patients; one size does not fit all	With HTE, evidence based on specific patient is essential to personalize treatment decisions (e.g., serotonin reuptake inhibitors for treatment of depression)	Homogeneity of treatment effects (e.g., insulin [titrated to need] for reduction of blood glucose)
Chronicity	Long-term treatment for chronic condition	Chronicity allows knowledge gleaned from single-patient trials to inform future treatment decisions (e.g., gastroesophageal reflux disease)	Acute conditions (e.g., influenza) One-time treatment with long-lasting effects (e.g., surgery)
Stability	Stable treatment effect *	Stability ensures that knowledge gleaned from single-patient trials informs future treatment decisions	Lack of stability (e.g., in an individual whose dietary intake of vitamin K fluctuates widely over time, the effects of warfarin may be unstable relative to the effects of aspirin)
Effect onset and carryover	Transition periods between two treatment periods may be needed for the effect of previous treatment to extinguish, and the effect of new treatment to commence and stabilize. Insufficient length of either might confound estimation of long-term treatment effect	Negligible or modest duration for onset and carryover (e.g., short-acting psychostimulants for ADHD) allows single-patient trials to provide valid knowledge about long-term treatment effect, especially when accompanied with appropriate washout or analytic strategies to untangle slow onset and carryover effects from long-term treatment effect	Long duration of onset and/or carryover (e.g., long-acting medications)
Lack of adequate evidence	Existing clinical evidence not adequate to inform treatment decision for individual patients	Lack of adequate evidence creates the need for evidence to be gleaned from single-patient trials (e.g., effectiveness of prophylactic antibiotics in spinal cord injury patients with frequent urinary tract infections)	Adequate evidence: there is no need for further evidence from single-patient trials (e.g., effectiveness of HMG-CoA reductase inhibitors [statins] for reduction of cardiovascular risk in individuals with established coronary artery disease)

Abbreviation: ADHD, attention-deficit hyperactivity disorder.

* The assumption of stable treatment effect is weaker than the assumption of stable treatment outcome under both treatments. With the assumption of stable treatment effect, it is possible for treatment outcome to manifest a time trend, say, a gradual deterioration over time, as long as the trajectories are parallel for the two treatments, so that the difference between the treatments remains constant (stable). In other words, this assumption amounts to a requirement that treatment effect and time trend are additive that is, there is no treatment × time interaction.

Table 3: Indications and contraindications for N-of-1 clinical trials (modified), depicted from Duan N. et al. [62]

4.4.1. Comparison of „N-of-1 Clinical Trials“ vs. "Therapeutic Trials"

“Therapeutic trials” are defined as therapeutic interventions to evaluate the effectiveness in individual patients and have been utilized extensively in clinical practice. Such interventions as part of the usual care, are sensitive to bias as they are unblinded, have no control conditions, and involve no formal validated assessment of effectiveness. In contrast, „N-of-1 clinical trials“ include prospectively planned interventions with predefined data assessment and multiple comparisons with a control substance, usually an alternative treatment option or placebo.

4.4.2. Study Design and Relevant Indications

N-of-1 trials in clinical medicine are composed as multiple crossover trials prescribing sequential episodes of treatment A (verum) or treatment B (e.g. standard of care, placebo, no treatment) performed in a randomized or balanced and double blinded fashion including the systematic measurement of results as displayed in Figure 7.

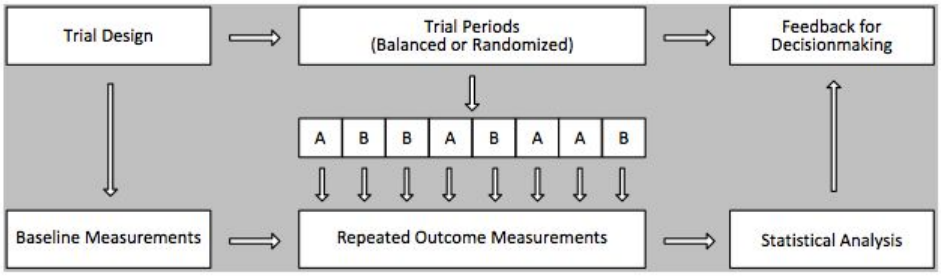

Figure 7: Scheme for a prototypical N-of-1 Trial (modified from Zucker et al. [63]

„N-of-1 clinical trials“ have been conducted in a broad variety of indications such as rheumatism [63], chronic neuropathic pain [64], dyspnea [64], chronic obstructive pulmonary disease (COPD) [66], oncology [67] and pediatric indications [68], [69].

It is interesting to note, that the „N-of-1 Clinical Trial Concept“ may be the only suitable trial design to study treatment options for diseases with low or very low prevalence (Orphan Diseases) due to the limited availability of patients qualifying for traditional RCTs. The „Orphan Designation“ status is granted, if less than 1 in 2.000 citizens (Europe) [70] or less than 1 in 1.500 citizens (USA) [71] are affected by a distinct medical entity, usually a disease or syndrome described and recognized by international organizations such as the “International Classification of Disease” (ICD) issued by the “World Health Organization (WHO) [72].

The relevance to assess new treatment concepts for rare diseases becomes evident, as more than 6800 different conditions qualify as orphan diseases representing 6-8 % of the total population in both regions, Europe and USA [73], [74]. Although each orphan disease may require a unique scientific and clinical approach, they frequently share similar methodological challenges. The development of patient centric treatment options supported by the precision medicine initiatives resemble the needs observed previously in clinical trial designs and statistical methods for orphan diseases.

4.5. Summary: The Evolution of Clinical Trial Concepts

The "Randomized Controlled Trial" (RCT) is considered the "gold" standard to assess the efficacy and safety of IMPs / INDs. As the RCT approach is applied to study the prevention, diagnosis and treatment of diseases and to assess the quality of life, multiple designs were developed over time to address different objectives of the trial portfolio. The PM concept, supported by the public initiatives in the EU and USA, incorporated new parameters such as genetic variations, environmental and lifestyle factors to prevent and treat diseases. "Basket"- and "Umbrella" trial concept include molecular signatures obtained from biopsies to assign individual patients to defined treatment groups in clinical trials. However, the stratification of patients according to biomarkers might prove to be of limited applicability, as the number of potential molecular targets for therapeutic intervention is expected to increase further as one of the outcomes of future biomedical research. Therefore, the identification of patients, who display a similar or identical molecular profile as one of the crucial inclusion criteria to qualify for a particular treatment arm, could render an important obstacle to successfully recruit study cohorts. From a conceptual point of view, the N-of-1 clinical trial approach could provide a suitable solution, as the individual patient is the sole subject of clinical trials. Table 4 summarizes advantages and disadvantages of N-of-1 trials at the indicated phases of clinical development.

N-of-1 Trial	Phase I	Phase II	Phase III	Phase IV
Pros	No advantage over current approaches to address safety and tolerability in healthy volunteers. Oncology patients might benefit as multiple drugs / drug combinations are tested in a short timeframe to assess safety and tolerability.	Suitable approach for PoC studies to demonstrate efficacy or lack of efficacy related to individual molecular signatures. Participants having an opportunity to experience active therapy, not just placebo.	Significantly lower costs. Participants will receive their results more quickly than in standard RCTs (e.g., months instead of years) and the results will be relevant and applicable to the participants themselves. Suitable trial design to study rare diseases or pediatric indications where limited patient numbers are recruitable.	Excellent approach for comparative effectiveness research (CER) and patient-centred outcome research (PCOR). Possibility to evaluate the therapy at initiation incl. periodic reevaluation to ensure ongoing effectiveness.
Cons	Unnecessary risk for healthy volunteers.	Requires significant investment into biomarker development as the availability of reliable diagnostic and prognostic markers is mandatory to demonstrate efficacy.	New statistical methods required. No clinical endpoints, study results are based on surrogate endpoints only. Comprehensive molecular profiling data of patients required to match individuals to the optimal treatment regimen.	Strictly standardized clinical procedures required to ensure comparability of clinical results and to allow for meta-analysis on N-of-1 trial data.

Table 4: Description of advantages and disadvantages of the N-of-1 clinical trials concept at different phases of clinical development

Part II: Challenges for Clinical Development Programs Implementing N-of-1 Clinical Trials

5. Organizational, Technical and Scientific Requirements:

Adopting precision medicine in research and in daily care requires profound changes to the infrastructure and mechanisms for data-collection, -storage and -sharing to *„create a continuously learning health care system with seamless cycling between clinical care and research*“ [75]. Aronson and Rehm strongly advocate the creation and refinement of a „Precision Medicine Ecosystem“ linking clinics, diagnostic laboratories, research enterprises, and relevant databases together as depicted in Figure 8 below.

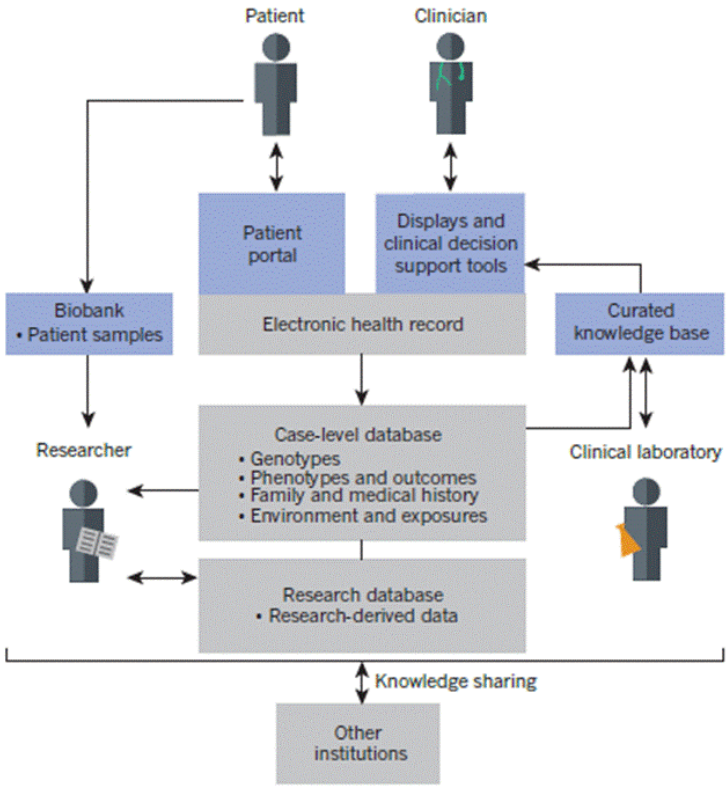

Figure 8: Scheme of a potential precision medicine ecosystem, depicted from Aronson and Rehm [74]

5.1. Organizational Framework

Clinical trials in the European Union and the United States of America are predominantly sponsored by industry, academia-, and government-institutions. Over the last decade patient recruitment has shifted towards a global open enrollment system to manage the increased number and size of clinical trials. Concurrently, developed countries including the USA became less attractive to execute clinical trials, predominantly for cost reasons. As the nationwide capacities and capabilities are diminishing, Weisfeld et al. [76] advocate development of a sustainable and continuous national clinical trials infrastructure in the USA to perform innovative clinical trials providing the scientific evidence for rational clinical practice and break-through treatments. Although the sponsors, investigators, and the purpose of clinical trials vary considerably, there are common aspects that help to ensure a high quality standard and reduction in cost of clinical trials. The key elements listed in Table 5 below could provide a framework for a sustainable and continuous clinical trials infrastructure to conduct US-based RCTs.

- Investigator recruitment
- Experienced clinical trial personnel
- Protocol development support
- Regulatory approval to conduct the clinical trial (e.g., Investigational New Drug [IND] applications in the United States)
- Good Clinical Practice (GCP) requirements (primarily for interventional clinical trials), including
    - informed consent,
    - ethical review,
    - human research participant protections,
    - privacy considerations,
    - investigator training and qualifications, and
    - adverse event (AE) reporting
- Contractual agreements between sponsors, institutions, and investigators
- Participant recruitment plan
- Coordination of clinical trial investigators and centers both in the United States and globally
- Quality-control systems to ensure GCP compliance
- Data collection, management, and analysis
- Data standards (e.g., medical concept coding, diagnosis coding, data standards)
- Communication of results (publication)
- Registration of clinical trials and results on https://clinicaltrials.gov/

Table 5: Key elements to be addressed by a clinical trials infrastructure (modified), depicted from Weisfeld et al. [76].

Eisenberg et al. [77] further define additional potential areas that would benefit from a national clinical trials infrastructure such as the topics listed in Table 6.

- Investigator Training
  - training protocols with standardized core content and the availability of „Continuing Medical Education“
  - centralized certification processes for clinical investigators
- Investigator Recruitment
  - information technology (IT) solutions for matching investigators to sponsors
  - development of investigator networks including primary care and specialty/academic care
  - development of novel approaches to clinical trial design
- Investigator/Clinical Trial Staff Support
  - standardized contracts to accelerating the contracting and subcontracting in clinical trials
  - standardized approach for the reimbursement of medical expenses
  - management of privacy issues to facilitate observational trials
- Regulatory Approval
  - development of a globally harmonized regulatory database, nomenclature, and identification of clinical trials involving investigational molecules or devices
  - centralized institutional review board (IRB) review for „Multi Regional Clinical Trials“ (MRCTs) to enhance the protection of study participants
- Recruiting Clinical Trial Participants
  - patient education as part of education of the general public about the benefits of clinical trials for innovative and improved treatment options
  - disease-specific and consumer friendly solutions for aggregating clinical trial reporting to improve the public understanding of the value of participating in clinical trials
  - pre-identification of individuals interested to participate in clinical research by e.g. providing a card, similar to an organ donor card
  - integration of electronic health records with clinical trial databases combined with an alert system to inform patients and physicians when individual health conditions meet criteria for enrollment in a clinical trial
  - development of a patient-friendly interface with e.g. https://clinicaltrials.gov/ including user friendly search options
- Conducting Clinical Trials
  - clinical trial identifier standards for identification of patients/trials in „Electronic Medical Records“ (EMRs). Harmonized data standards for use in clinical research should be mapped to electronic health records to facilitate screening
  - development of a centralized electronic tool for notifying investigators, regulators, and IRBs of e.g. „Adverse Events“ (AEs), „Serious Adverse Events“ (SARs), „Suspected Unexpected Serious Adverse Events“ (SUSARs), clinical trial amendments, and substantial amendments
  - online protocol-authoring tools and templates to create more uniform protocol formats and thus facilitate the correct implementation of research protocols by research staff
  - global harmonization of regulatory requirements for AE reporting to agencies, investigators, and IRBs to reduce clinical trial complexity and cost e.g. adoption of the „Development Safety Update Report“ (DSUR) format
  - continued development of guidance documents relating to clinical trial design, endpoints, and other key considerations
  - alignment of global AE reporting to regulators vs. investigators to increase the efficiency and effectiveness of clinical trials, especially trials conducted at multiple international sites.
  - Online management of informed consent and informed consent updates

Table 6: Additional potential areas that would benefit from a national clinical trials infrastructure (modified), depicted from Weisfeld et al. [77]

The list of summarized topics above described by Eisenberg et al. provides a framework for the USA which is also relevant for the EU. The novel clinical trials - Regulation EU No 536/2014 [47] addresses some topics listed to facilitate „Multi Regional Clinical Trials“ (MRCTs) across the EU by creating a harmonized application procedure via a single EU portal/database replacing https://eudract.ema.europa.eu/. Moreover, defined timelines for the assessment and approval of „Clinical Trial Applications“ (CTAs) by regulatory authorities and ethical committees, and the reporting of SUSARs (see chapter 4.1) will be implemented. However, there is currently no discussion in the EU to create a suitable publically funded research infrastructure on EU level to support innovative approaches e.g. as part of the EU precision medicine initiative. Such a public investment would also substantially facilitate patient centric research approaches like N-of-1 clinical trials in Europe.

5.2. Information Technology Infrastructure and Data Management for Clinical Trials

N-of-1 clinical trials have not been used broadly in the past despite the potential for patient care and to reduce cost [78]. As discussed in the previous chapter, an EU wide organizational infrastructure would be greatly beneficial for improving health care systems in the EU-MSs by focusing on patients‘ needs. As part of such an endeavor, the implementation of an adequate information technology infrastructure is considered mandatory to be effective and efficient for patients and their clinicians by implementing automated workflows to limit costs.

As „*existing clinical trial management systems are inadequate for managing N-of-1 trials*“ [79], Eslick and Sim describe an IT system named MyIBD, which „was developed by the Cincinnati Children’s Hospital and Medical Center (CCHMC) and a third-party consulting group (including author I.E.) as part of its Collaborative Chronic Care Network (C3N) health services research project“ [79]. They targeted a minimal set of requirements to facilitate the definition and management of up to 100 concurrent, independently designed n-of-1 trials“ based on predefined requirements displayed in Table 7.

Features supporting n-of-1 trials

- Record clinician goals and patient goals
- Document the experimental hypothesis
- Protocol implementation support
    - Library of characterized treatments (including details of onset, carryover, etc.)
    - Library of characterized measures (including precision and variance)
    - Support for randomization
    - Web service connections to acquire/share libraries of standard measures
- Trial protocol specification
    - Choice of characterized treatments
    - Choice of measures
    - Choice of duration and number of treatment periods
    - Decision on important covariates to track
    - Analytical design

• Connection to Electronic Medical Records (EMRs), Personal Health Records (PHRs), pharmacy records (obtained medication context, lab reports, etc.)
• Data collection and user engagement support
    - Data capture modules (e.g., choice lists, visual analog scales)
    - Applications programming interfaces (APIs) to third-party data services such as sensors, apps (e.g., for symptom tracking)
    - Direct email or Short Message Service (SMS) submission of patient-reported outcomes (PRO)
    - Trial progress review screens for patients and clinicians, and other user engagement modules (e.g., leaderboards, rewards)
• Data analysis and review
    - Data preprocessing modules
    - Statistical analysis modules
    - Visualization modules
    - Data review and decision-support modules

Institutional support for N-of-1 trials
• Integration with electronic health records (EHRs) for recruiting and screening
• Configurable eligibility requirements
• Support for external informed consent processes and documentation requirements
• Population review
• Summary reports (e.g., participation, utilization)

Aggregation of N-of-1 trial results
• De-identification of patient record (for real-time in situ analysis, or for download to external systems for secondary analysis)
• Statistical analysis and aggregation of raw individual patient-level data
• Statistical analysis and aggregation of summary results data
• Statistical analysis and modeling of aggregated outcomes
• Models for using aggregated group outcomes to facilitate "borrow from strength" for individual treatment effects and to estimate individual-level heterogeneity of treatment effect

IT infrastructure
• Secure data storage
• Data transmission security
• Data downloading in multiple formats
• Authorization controls (who can do what)
• De-identified views of data

Table 7: Requirements of an N-of-1 Trial platform, depicted from Eslick I., Sim I. [79]

The development costs for the IT system are expected to exceed $ 250,000 with monthly infrastructure and maintenance costs of $ 400 and monthly support contract costs of $ 1000.

Eslick and Sim expected, that the upfront investment will be offset by minimized per-patient cost enrolling into N-of-1 trials.

5.3. Biobanking and Analysis of Clinical Samples

During the last decade, multiple definitions for biobanks or biorepositories were published. The „Organization for Economic Co-Operation and Development“ (OECD) defines a biobank as *„a collection of biological material and the associated data and information stored in an organized system, for a population or a large subset of a population“* [80]. The „Merriam Webster Medical Dictionary“ gives a narrower definition and specifies a biobank as *„a storage place for biological samples (such as human tissue, blood, or DNA) that may be used especially for future medical research*“ [81].

Generally biobanks comprise three categories of information:

- biological human material
- additional information that is associated with the sample
- legal documents such as individual consent declarations and features to ensure data safety and privacy

A comprehensive overview on biobanking related activities in Europe was published by the „Joint Research Center“ (JRC) of the EC [82]. A global directory of biobanks, tissue banks and biorepositories is available on „Specimencentral.com“ [83].

The „Pan-European Biobanking and Biomolecular Resources Research Infrastructure“ (BBMRI) distinguishes between two types of biobanks:

- Population-Based Biobanks: *„The most common format is the longitudinal population-based biobank with biological samples and data from randomly selected individuals of a general population. Typically, blood or isolated DNA together with data about family history, lifestyle, environmental exposure, etc., are collected at the entry time point into the study and at certain time points during follow-up*“ (Table 8) [84], and

- Disease-Oriented Biobanks: *„In contrast, in disease-oriented biobanks, which may contain tissue, isolated cells, blood or other body fluids, specimens which are collected from an individual in the context of medical diagnosis and treatment*“ (Table 8) [84].

Biobank format	Application/specific strength
Population-based biobanks	
Longitudinal population-based biobanks	• Prospective approach allows high level of standardization • Reduced selection bias • Determination of the natural frequency of occurrence of diseases • Good characterization of environmental exposure • Identification of predictive biomarkers
Population isolates	• Fewer variables for the identification of genetic risk profiles • Traceable family histories
Twin registries	• Efficient comparison between genetic and environmental risk factors
Disease-oriented biobanks	
Clinical case–control studies	• High number of diseases represented allow insight into variations of diseases and the study of rare diseases • Studies can be initiated soon after launch with lower cost • Comprehensive clinical characterization of diseases • Identification of biomarkers for patient selection
Tissue banks	• High number of diseases represented allow insight into variations of diseases and the study of rare diseases • Studies can be initiated soon after launch with lower cost • Identification of biomarkers for patient selection • Investigation of localized diseases or organ-specific manifestation of systemic diseases • Corresponding normal and diseased tissue from the same individual allows discrimination between acquired disease-related alterations and genetic background

Table 8: Major biobank formats with their typical applications and specific strengths, depicted from Asslaber M. and Zatloukal K. [84]

5.3.1. Tissue Acquisition and Storage

The OECD provided „Guidelines on Human Biobanks and Genetic Research Databases“ for „*the establishment, governance, management, operation, access, use and discontinuation of human biobanks and genetic research databases (“HBGRD”), which are structured resources that can be used for the purpose of genetic research and which include: (a) human biological materials and/or information generated from the analysis of the same; and (b) extensive associated information*“ [85]. Furthermore, the EU also issued a concept paper on „Biobanks in Europe: Prospects for Harmonization and Networking“ [86] and the „National Institutes of Health“ (NIH) published „NCI Best Practices for Biospecimen Resources Recommendations on Research on Human Biological Materials“ developed by the U.S. National Cancer Institute (NCI) [87].

As displayed in Fig. 8, biobanks represent a core component of precision medicine. However, due to the lack of standardization, individual biobanks are organized with variable goals, governance and structures, thus impairing the analysis and exchange of data. With regards to ethical aspects of biobanking, only national laws and guidelines are adhered to of the country where the biobank is physically located. Consequently, the implementation of non-harmonized informed consent concepts resulted in the restriction of global use of these repositories. Another important barrier to European networking or the lack thereof is the differences in data protection measures in the EU-MSs due to non-harmonized definitions and wording of domestic legal documents implementing the data protection Directive 95/46/EC [88]. While this directive serves at least as a benchmark for the exchange and flow of data, the European Commission has

no authority to regulate the exchange of scientific samples as this part of legislation refers to national property law in many EU-MSs. Experts widely recognize the need for an umbrella organization to improve collaboration and networking among the existing biobanks and to contribute suggestions for novel regulatory requirements facilitating pan-European research. Topics of interest for the experts include how „*common operating procedures can be established for practices such as genotyping and phenotyping, quality assurance, information management. Related legal and ethical issues (type of consent, privacy protection, feedback of information to donors, etc.) must also be considered. In particular, harmonization of data collection and management methods is of crucial importance in order to guarantee an even and high quality of the data stored in the databases*“[89].

5.3.2. BIO-RAIDs – an EU Study Protocol in Cervical Cancer (CC)

Although researchers in Europe face substantial problems exchanging samples and associated data with regards to the sample/data dichotomy, the so-called BIO-RAIDS study design exemplifies how the precision medicine approach could be applied in clinical trials across multiple EU-MSs (Clinicaltrials.gov: NCT02428842, registered 10 February 2015). „*BIO-RAIDs is a prospective multicenter European study, presently recruiting patients in 6 EU countries. Tumor and liquid biopsies from patients with previously non-treated cervical cancer (stages IB2-IV) are collected at defined time points. Patients receive standard primary treatment according to the stage of their disease. 700 patients are planned to be enrolled. The main objectives are the discovery of -dominant molecular alterations, -signaling pathway activation, and -tumor micro-environment patterns that may predict response or resistance to treatment. An exhaustive molecular analysis is performed using 1° Next generation sequencing, 2° Reverse phase protein arrays and 3° Immuno-histochemistry*“ [90]. The clinical trial is conducted in accordance with the principles of the „Declaration of Helsinki“, the ICH-E6 „Good Clinical Practice“ (GCP) guideline, national laws and regulations and approved by ethic committees and regulatory authorities of the participating countries France, Germany, Moldavia, Netherlands, Romania and Serbia.

Patient recruitment, inclusion / exclusion criteria, diagnosis, and standard treatment of cervical cancer are strictly defined, standard operating procedures for biopsy handling, blood and sera collection were established by the RAIDs consortium and all samples are stored at a central biobank. The operational sample flow is shown in Figure 9 below.

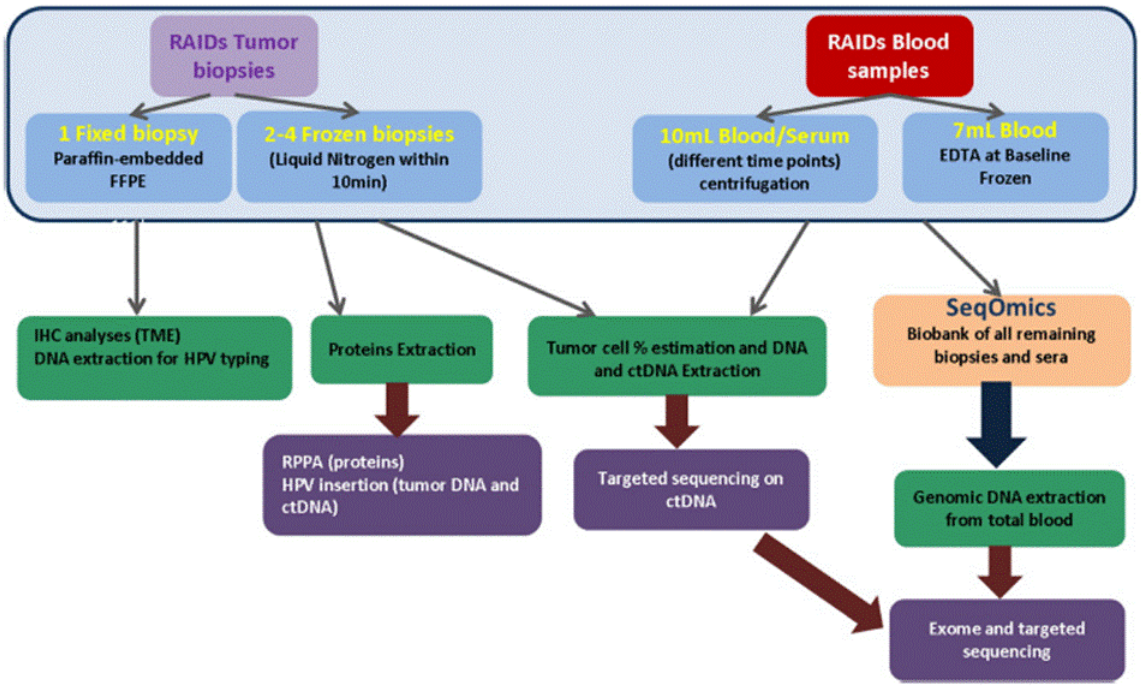

Figure 9: Sample Flow. Patient blood samples and biopsies are centralized at local centers and then sent to research platforms, where the material will be processed and analyzed by different methods (IHC, HPV insertion, sequencing, RPPA). Centralized biobanking of the remaining material will be performed at seqOmics (Hungary), depicted and modified from Ngo C. et al. [90]

Data analysis will be performed as displayed in Fig. 10 below to identify driver mutations and pathways activated in cervical cancer (CC) as well as biomarkers to predict complete response, progression free survival and overall survival.

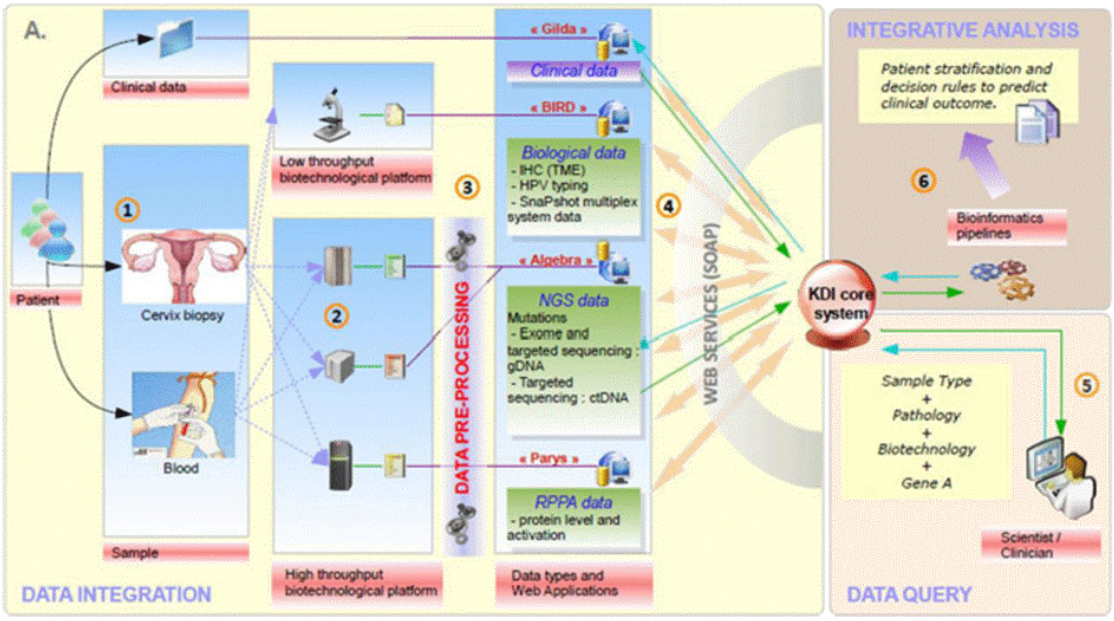

Figure 10: Knowledge and Data Integration (KDI). Integration of heterogeneous clinical and biological/molecular data requires a powerful information system. Data integration: all data (clinical data from eCRF, biological data, including tumor microenvironment (TME) analysis using immunohistochemistry (IHC) and HPV typing and raw data from technological platforms: The data obtained from exome- and targeted sequencing on gDNA and ctDNA, and reverse phase protein analysis (RPPA) will be integrated into the KDI core system. Afterwards advanced research functionalities will enable multiple data queries. Specific bioinformatics pipelines will generate new integrative knowledge from these heterogeneous sources of data (figure adapted from Servant et al.), depicted and modified from Ngo C. et al. [90]

However, as expected of all new concepts, the implementation of BIO-RAIDs in the participating countries was significantly delayed by multiple factors such as regulatory aspects, insurance modalities, negotiation of sponsorship delegation contracts, site-specific logistics for biobanking, and clinical trials operational management. Nevertheless, the scientific infrastructure and methodology that was developed as part of the study, as well as lessons learned, may prove as a suitable framework for future precision medicine clinical trials. Furthermore, data collected from genotype / phenotype correlation analysis, responses to treatment and the identification of diagnostic and prognostic biomarkers may be used to stratify cancer patients for the most appropriate therapy, with N-of-1 clinical trials being one of the possible options. Figure 11 displays a decision tree proposal with guidance criteria for selecting the most suitable clinical trial concept.

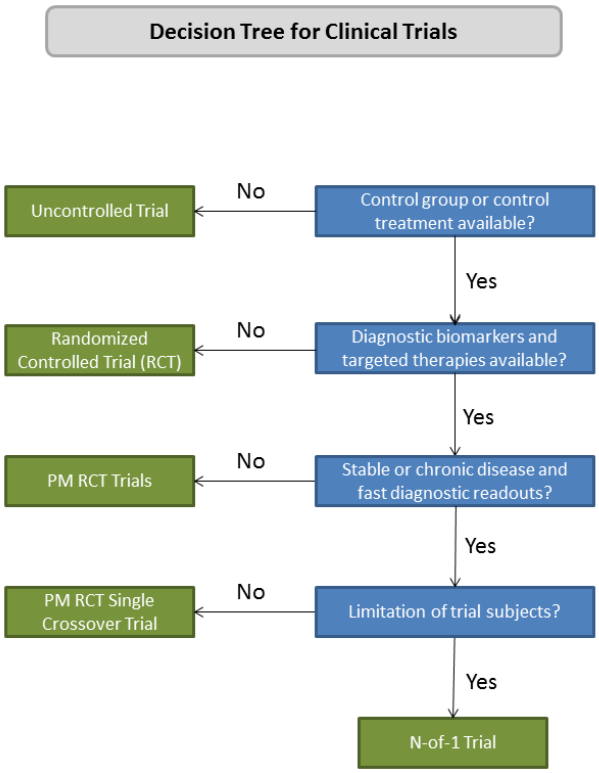

Figure 11: Decision tree with proposed guidance criteria for selecting suitable clinical trial concepts.

5.4. Biostatistics:

5.4.1. Statistical Analysis in Clinical Trials

The statistical principles relevant for clinical trials are described in the ICH Guideline E9 [91]. Sampling is defined as the selection of individual observations intended to yield some knowledge („estimate“ plus associated „error“) about a population. „Simple random sampling“ is the basic sampling technique where a group of subjects (a sample) is selected from a larger group (a population) for study purposes. Each individual is chosen entirely by chance and each member of the population has an equal chance of being included into the sample. Simple random sampling ensures, that the sample chosen is representative of the population and that the statistical conclusions will be valid. The measurement values of a defined quantity in a large number of individuals are called „distribution“. With increasing sample number (n-number), the sampling distribution of sample means approaches the pattern of a „normal distribution“ with a mean identical to the population and a standard deviation (σ) equal to the standard deviation of the population divided by the square root of the sample size „n“ (Central Limit Theorem). As a reference, the mean +/- 2 σ represents 95.4% of the normal distribution. The variance (Var) equals σ^2.

The number of patients required for a study to obtain a high probability to detect the expected quantitative effect depends on several factors such as the

- expected quantitative effect of the treatment
- estimated variability of the effect
- required significance level
- desired power of the study

As the actual quantitative effect and the variability of the treatment depends on the drug profile, prespecified inclusion- and exclusion-criteria for study acceptance, and the individual biological and clinical characteristics of the enrolled study members, the „significance level“, (type I error) usually set at 0.05 (5%), describes the probability that an ineffective treatment will be declared to be effective (consumer‘s risk). A low significance level requires a high sample number.

The „power“ (type II error), usually set at 0.8 (80%) and 0.9 (90%), describes the probability of the study to detect the difference of interest and therefore the likelihood of declaring an effective treatment to be ineffective (producer’s risk). A high power requires a high sample number.

Study Data analysis includes

- hypothesis testing
- calculation of p-values
- calculation of confidence intervals
- interpretation of results

Hypothesis testing:

The null hypothesis (H0) is set a priori. If the trial aims to detect a difference, the null hypothesis H0 states e.g. that there is no difference between the new treatment and placebo and the distributions are not significantly different. The “alternative hypothesis” (H1 or HA) is the hypothesis of interest and states that e.g. the new treatment is better than placebo resulting in a distribution shift

Type I and Type II error:

The type I error is of critical importance to regulators during the assessment of study data and needs to be met with a nominal significance level set to 5%. Since testing is only performed in one direction in terms that the verum provides better results than the comparator and not different (better or worse) results, the type I error needs to be set to 2.5% (one-sided), to avoid an increased probability that an ineffective treatment will be declared to be effective. The p-value describes if „H0“ is true. The ICH Q9 guideline states that “*the issue of one-sided or two-sided approaches to inference is controversial and a diversity of views can be found in the statistical literature. The approach of setting type I errors for one-sided tests at half the*

conventional type I error used in two-sided tests is preferable in regulatory settings. This promotes consistency with the two-sided confidence intervals that are generally appropriate for estimating the possible size of the difference between two treatments." Type II errors are less critical for regulatory purposes but will contribute to the assessment of ethical considerations and safety concerns.

Confidence Intervals:

Demonstrating statistical significance AND clinical relevance is necessary to obtain marketing authorization for a medicinal product. The actual degree of the difference between two treatment alternatives is important to define the clinical relevance and contributes significantly to the "benefit-risk" evaluation.

Interpretation of results:

Generally two pivotal trials are required to demonstrate efficacy and safety of the MP under investigation. Nevertheless, „*there is no formal requirement to include two or more pivotal studies in the phase III program, however in most cases a program with several studies is the most, or perhaps only feasible way to provide the variety of data needed to confirm the usefulness of a product in the intended population. In the exceptional event of a submission with only one pivotal study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency*"[92]. It is important to consider that, in order to provide the same statistical evidence, a single trial would require significance levels 2-sided of $p<0.00125$ or 1-sided of $p<0.000625$ compared to two positive trials with significance levels 2-sided of $p<0.05$ and 1-sided of $p<0.025$.

5.4.2. Statistical Considerations for N-of-1 Clinical Trials

As described previously in chapter 4, „Randomized Controlled Trials" (RCTs) are designed to ensure that each study group represents a random selection of the potential user population with regards to known and unknown clinically relevant parameters.

N-of-1 trial designs aim to balance the assignment of treatments (A vs. B) over time to avoid the treatment effect to be influenced by systematic error. A single treatment sequence AB or BA would not rule out random error or time-dependent confounding factors. The influence of exogenous factors such as diet, physical activity, and stress or time-by-treatment interactions can be eliminated by repeating the treatment sequences, whereby the number of repetitions in a N-of-1 trial will correlate with the sample size of a parallel RCT design.

However, a treatment design such as AAAABBBB would not protect against linear time dependent effects such as long-term trending. The randomization of treatment periods or the application of „Paired Design" (ABABABAB) or „Single Counterbalanced Design" (ABBAABBA) would prevent random effects and linear bias. The „Double Counterbalanced Design"

(ABBABAAB) as displayed in Fig. 7 avoids linear and non-linear confounders to affect the treatment outcomes and is considered the optimal design for N-of-1 clinical trials [63].

A „run-in“ period prior to the randomized or balanced treatment sequences could be applied to identify interindividual variabilities such as responders and nonresponders or to define the initial starting dose. Multiple crossover clinical trials entail the risk, that „carryover effects“ could impair the validity of measurements beyond the crossover date of treatments. The value and suitability of washout periods intercepting individual treatment blocks is subject to controversy [93]. While statistical models are designed to accommodate carryover effects, they rely on assumptions based on pharmacokinetic (PK) and pharmacodynamic (PD) data and the length of the therapeutic treatment blocks A and B, but all of them are considered inferior to designing appropriate washout periods based on pharmacokinetic data [94].

Significant ethical concerns may arise, if scheduled washout periods will result in off-treatment phases for patients who already experienced benefits from both treatments options, e.g. when investigating A (verum) vs. B (standard of care). The „Evidence-Based Medicine“ (EBM) Working Group of the „American Medical Association“ (AMA) concludes that „N of 1 randomized controlled trials“ provide the strongest evidence for decision making to treat individual patients [95]. However, N-of-1 concepts have not yet been widely applied since specific requirements need to be fulfilled, such as i) chronic or frequently reoccurring clinical conditions, ii) short half-life of the medication to be tested and iii) fast readouts to evaluate for clinical effectiveness [62].

Furthermore, the statistical analysis of the data remains challenging. Parametric tests such as Z-test, two samples t-test, paired t-test and variance analysis were applied to analyze N-of-1 trial data [96]. In order to calculate the pooled treatment effect for more than two subjects Zucker et al. [97] performed meta-analysis of summary data, Huber et al. [98], Higgins et al. [99], and Jones et al. [100] applied linear mixed models to perform meta analysis of indivduals‘ data while accounting for correlations deriving from study members, and Schluter et al. and Zucker et al. [101], [102] applied mixed effect models.

The ICH E9 guideline [90], currently under revision [103], was adopted by the EMA and FDA and defines the current requirements in ICH countries to prove superiority vs. a comparator, usually placebo. The ICH E10 guideline on the „Choice of Control Group and Related Issues in Clinical Trials“ [104] states that „*in cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control*“. The EMA and FDA issued guidelines to demonstrate „non-inferiority“ to compare new treatments with active controls e.g. „standard of care“ which are also frequently performed in oncology related N-of-1 clinical trials [105], [106], [107]. The expanding experience on clinical trials involving small patient numbers and the application of new statistical methods to analyze clinical data should be considered a starting point for further revision of the ICH E9 and ICH E10 based guidelines to reflect the current discussion in literature on the statistical analysis of N-of-1 clinical trial data.

5.5. Companion Diagnostics: Molecular Profiling for Selecting and Monitoring Patients

As discussed previously in chapter 2.2, the co-development of a new pharmaceutical product and their corresponding test system are crucial to establish precision medicine approaches in health care systems. „In Vitro Companion Diagnostic Devices“ are defined as tools that provide information essential for the safe and effective use of a corresponding chemical or biological drug product. The tests are intended to identify a biomarker-defined subset of patients that are most likely to benefit or are at increased risk of serious adverse reactions and therefore excluded from treatment. Furthermore, continuous monitoring of the response to a distinct therapy will allow for treatment adjustments to increase safety or effectiveness. The FDA requests a contemporaneous development and acts as a „One-Stop-Shop“ for approving therapeutic products and their corresponding medical devices and/or test systems.

The authorization to commercialize „Medicinal Products“ (MPs) and „Medical Devices“ (MDs) in the EU follows two separate pathways. The EU has developed a flexible concept for MPs, whereby the applicant is requested to select one out of four licensing procedures given, namely i) “Centralized Procedure” (CP) [108], ii) “Decentralized Procedure” (DCP) [109], iii) “Mutual Recognition Procedure” (MRP) [109], and iv) “National Procedure” (NP) [109], [110], taking into account defined regulatory obligations and the intended strategy for commercialization. Placing MPs on the market requires a marketing authorization by a „National“ or „European Regulatory Authority“. MDs require a “Conformité Européenne” (CE) number issued by the manufacturer or nationally designated organizations of the EU-MSs, named „Notified Bodies“ (NB) based on risk categorization. The risk-assessment procedure approach includes three different classes (I, II, III) and two subclasses (IIa, IIb) reflecting the intended primary „Mode of Action“ (MoA) and the vulnerability to the human body. Individual risk classes require different levels of technical documentation and conformity assessment procedures.

The increasing number of marketing authorization approvals for i) targeted therapy drug products requiring companion diagnostics and ii) drug device combination products such as „*drug-delivery products and medical devices incorporating, as an integral part, an ancillary medical substance or an ancillary human blood derivative*” [111] revealed, that the qualification of the NBs and their assessment procedure for certifying MDs do not match the standards required to ensure the safety of patients particularly related to molecular profiling by *in-vitro* diagnostic (IVD) tests and treatment via drug-device-combination products.

A revision of the current legislation is even more important, as „Health Technology Assessment“ (HTA) bodies of individual EU-MSs started independently to investigate combinations of individual pharmaceuticals and IVD tests for detecting patients most likely to respond to specific drugs with the intention to reduce health care expenditures. HTA bodies decide in many EU-MSs if, or to which extent, pharmaceuticals and other healthcare products are reimbursed by the „Statutory Health Insurance“. As the overall majority of innovative pharmaceuticals are authorized via the CP, the evaluation of corresponding MDs e.g. IVD companion diagnostic tests, based on common scientific grounds would be mandatory to ensure the optimal supply with

diagnostic tests and necessary equipment in all MSs where the drug product will be commercialized.

In order to reflect the recent technological and scientific advances, to address the identified deficiencies, and to overcome the different interpretations when the directives on MDs were translated into national law, the „European Commission“ (EC) proposed new „Regulations“, one for medical devices [112] and one for IVD devices and tests [113] in 2012 that will be binding for all EFTA states (EU + Iceland, Lichtenstein, Norway) and Turkey replacing the existing three directives [114], [115], [116]. The proposed legislation intends to ensure a high level of patient safety across the EU in a way that assessment- and certification-rules are consistently applied to manufacture and certify MD- and IVD-equipment with the necessary accuracy and reliability. The NBs are given authority to pursue unannounced inspections of manufacturing sites including subcontractors. The notifying bodies themselves will be confronted with much stricter accreditation requirements, joint assessments by teams from other EU-MSs and closely linked to national competent authorities, to which they will be accountable to.

It is foreseeable that the majority of IVD products will be upgraded from a classification needing only self-certification by their manufacturers to a class requiring assessment from a NB. Similar to medical devices, assessment of IVD tests will follow a risk-based approach. The clinical evidence to be provided will increase according to risk class and will include regular updates with clinical information obtained from post-marketing surveillance.

One important cornerstone of the revision will be the formation of the central „Medical Device Coordination Group“ (MDCG), comprised of national experts in medical and IVD devices. The MDCG will define the quality standards named „Common Technical Specifications“ (CTS) for the assessment of high-risk companion diagnostic products which in turn will be evaluated for CTS compliance by specially designated NBs on MS level. In a similar way the MDCG will define CTS for companion diagnostic devices. Compliance check CTS and certification will be performed by accredited „reference laboratories“.

The current revision of the MD and IVD legislation can only be a starting point for regulators to catch up with the rapidly evolving scientific development. With pharmaceutical companies reshaping their future value chain by investing significantly in the co-development of new „Medicinal Products“, corresponding „Companion Diagnostic Devices“ and „Molecular Tests Kits“, a regulatory framework providing one approval for all three components by a single authority would help to avoid redundant effort and parallel communication among stakeholders. The potential future requirement of a marketing authorization for high risk medical/IVD devices and tests is currently discussed, but unlikely to be part of the current revision. A new generation of drug-device combination products e.g. implants for the release of medicinal products, nanoparticles for targeted delivery of drugs into tumors and individualized therapeutic concepts comprising highly specific pharmaceuticals in combination with companion diagnostic equipment to treat (orphan) diseases are expected to require comprehensive clinical data packages for the MP and the MD component to obtain marketing authorization. Although the implementation of a „One-Stop-Shop“ architecture remains difficult to establish in the EU,

politics should aim to create an efficient regulatory environment to support future trends in medical care.

5.6. Summary: Organizational, Technical and Scientific Requirements

The N-of-1 trial design has the potential to become a prominent study tool in PM, if defined criteria are met. These criteria are disease- and treatment-related and include chronic or stable clinical conditions, the fast onset and termination of treatment effects and importantly, clinical relevance for the individual study participant in addition to the prospective benefit for public health as part of the benefit-risk-assessment. The adoption of N-of-1 clinical trials, Basket- or Umbrella-trials in clinical research require fundamental changes in public health care systems as they currently exist in developed countries. The implementation of an adequate IT infrastructure is crucial to create a "Precision Medicine Ecosystem" linking hospitals, diagnostic laboratories, biobanks and research- and clinical databases. Moreover, international harmonization of standards for tissue acquisition and storage, management of biobanks and associated data appears mandatory to fully utilize the continuously growing repositories on a global scale. Thorough scientific discussion on the application of statistical tools and the development of specific statistical methods are required as multiple approaches are currently applied to analyze small patient number- and N-of-1 clinical trials. However, the major challenge for the successful application of PM in clinical development from a biomedical point of view will be related to companion diagnostics. The co-development of diagnostic tests in conjunction with new medicinal products is a fundamental requirement to assess the safety and effectiveness of targeted therapies in individual patients.

6. Ethical Considerations and Regulatory Aspects:

6.1. Ethical Considerations:

6.1.1. The Declaration of Helsinki

The „Declaration of Helsinki" issued by the „World Medical Association" (WMA) defines ethical guidelines and principles for physicians, other participants and human subjects involved in biomedical research. With the first version issued in 1960 and adopted by the 18th WMA General Assembly, Helsinki, Finland in June 1964, the scientific development in biomedical research was accompanied by continuous adaptations. The „Declaration of Helsinki" version issued in October 2013 by the 64th WMA General Assembly in Fortaleza, Brazil, represents the current „*statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data*" [117].

Planned clinical studies are evaluated based on two fundamental principles. First, advancements in medicine are based on scientific research and should be supported by clinical research if justified from an ethical point of view. Second, the well-being of patients and healthy volunteers

has priority towards additional stakeholders representing scientific, social and economic interests. Furthermore, participants in clinical trials have comprehensive rights with regards to their personal data privacy with additional protection for minors and cognitively handicapped individuals. „Ethics Committees“ in the EU and an „Institutional Review Boards“ (IRBs) in the USA are independent bodies to enforce the rights of study participants and patients. A vote by these two institutions is always based on the individual evaluation of the CTA and balances the well-being of study participants and the prospective well-being of future patients who will benefit from improved treatment options.

6.1.2. Novel Ethical Duties

The implementation of the publicly funded „Precision Medicine Initiatives“ (PMIs) in the EU and US exemplify the new challenges. The PMI in the USA will create a cohort of 1 million volunteers contributing their health data and biospecimen to a centralized national database. The governmental initiators of the USA-PMI already addressed some of the ethical, legal, and social issues (ELSI) associated with the project, but Sankar and Parker [118] have judged that no research plan was defined for further ELSI investigations as the PMI develops over time. Vos et al. {119] conclude further, that the „*convergence of genomics, bioinformatics, and the collection of human tissues and patient data creates novel moral duties for researchers*“...as... „*the traditional research ethics principles aimed at protecting individual participants have become supplemented with social obligations related to the interests of society as unprecedented amounts of potentially sensitive information are being generated*“.

The authors have identified four different categories of moral duties genomic researchers need to be aware of:

Disclosure Duties: The application of genomics technologies generates personal data with probabilistic character and in many cases uncertain significance for the assessment of individual patients‘ health status. There is a growing consensus that researchers and clinicians are obliged to inform patients about genetic results that are i) analytically and clinically valid, ii) of clinical utility and iii) actionable in case the participant of the study has consented to disclosure [120]. The current discussion in the literature focuses on the definition of criteria for the disclosure of unsolicited findings, balancing the participants‘ interests and benefits and the interests of the society in advancing scientific knowledge.

Consent Duties: Recently, the concept of „informed consent“ as defined by the „Helsinki Declaration“ is increasingly challenged. The complex nature of genomic research limits the ability of study participants to understand content and meaning of the communicated scientific information. As an „informed“ decision depends on cognitive „understanding“ of the given facts, the concept of „appropriate“ consent emerged, such as broad consent, dynamic consent, tiered consent and opt out. The broad consent concept has been widely applied in genomic research and is most beneficial to support the scientific advancement, as it includes the permission to use clinical samples stored in biorepositories for future, not yet defined

experiments without further re-consent. It is evident, that the broad consent concept does not match the requirements of the „Helsinki Declaration“ to protect the autonomy of each study member being in „control of identifiable human material and data“.

Privacy Duties: Large genomic studies generate comprehensive personal data packages increasing the risk of individual identification. Third parties such as family members, employers and insurance companies could be potentially interested to get access, which in turn might result in illegitimate discrimination. The rigid protection of data privacy is considered a mandatory cornerstone to prevent study members from negative impairments on a personal level but also to augment the acceptance of the precision medicine approach in the general public. The obligation to protect privacy might be even higher for clinical research compared to clinical care, as clinical research has no primary focus to provide benefit for patients, but might lead to harm. On the other hand, personal information might be required to link genetic variants to disease status and progression, individual lifestyle and behavior. The anonymization of data would impair the identification of genotype-phenotype relationships as well as returning relevant genetic results to the study member.

Social Duties: Social responsibility includes data sharing on an international level to use public resources in an optimal way and to enhance the creation of generalizable knowledge especially on low-frequency genomic alterations. Researchers should be aware, that genomic studies need to include a wide range of subpopulations to ensure, that the health benefits of genomic research are relevant and accessible for all members of society.

Historically, clinical research ethics focused on the protection of individual study members reflected by privacy protection and informed consent policies. As part of precision medicine the researcher’s responsibilities are broadened and include disclosure duties by returning valid and relevant genomic data to study members and additional social duties such as data sharing and incorporation of subpopulations into genomic studies. Ethical conflicts are foreseeable, especially with regards to protecting individual privacy (privacy duty) and sharing data (social duty) and protecting privacy (privacy duty) and returning valid and relevant clinical data to the study member (disclosure duty).

The disparity between clinical research, defined as a process focusing on the generation of knowledge, and clinical practice, as a process focusing on the optimal health care for individual patients becomes less distinct as precision medicine advances. N-of-1 clinical trials are one example where patients are qualified and enrolled based on their genomic and metabolic profile. Participating in the optimal clinical trial increases the patient’s likelihood to already benefit from clinical research. Currently, there is no standard policy for regulatory or institutional approval of N-of-1 trials. „Institutional Review Boards“ (IRB) across the USA expressed different opinions, as to whether N-of-1 trials meet the definition of human subjects research as laid down in 45CFR46.102 requiring IRB approval. As N-of-1 trials are expected to become common practice as part of precision medicine clinical development programs, further clarification and guidance is required to ensure that the safety of participants will be evaluated based on harmonized criteria [121].

6.2. Regulatory Aspects

6.2.1. Data Extrapolation Concepts

Data extrapolation is defined as „*to infer values of a variable in an unobserved interval from values within an already observed interval*“ or with other words „*to project, extend, or expand known data or experience into an area not known or experienced so as to arrive at a usually conjectural knowledge of the unknown area*“ [122]. The EMA further specifies the term as „*extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product*“ [123].

Data extrapolation concepts are widely applied during pharmaceutical development, e.g.

- to project the safety and efficacy of new active substances for human beings based on non-clinical studies [124],
- to calculate the shelf life of drug substance and drug product using bracketing and martyring schemes [125],
- to facilitate pediatric drug development by avoiding unnecessary studies in children or optimizing decision making when patients are scarce [126],
- to evaluate safety and efficacy of drug products in subpopulations representing different ethnic groups to “bridge” the clinical data between the two regions [127] and,
- to expand the therapeutic indications for biosimilars with appropriate scientific justification, if biosimilarity with the reference product has already been demonstrated in one indication [128].

Biosimilars are a suitable group of medicinal products to exemplify the current case by case and agency by agency regulatory landscape. The marketing authorization approval of biosimilars, especially across indications, is granted based on the totality of data provided. Not surprisingly, regulatory authorities in different countries decide inconsistently whether to allow data extrapolation for a given biosimilar. „*The originator infliximab has wide approval for the indications of RA, AS, psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn’s disease. Biosimilars of infliximab have only been studied in the clinical disease populations of RA and AS. The EMA, FDA, and Korean regulators granted approval to the infliximab biosimilar Remsima / Inflectra for the full range of indications of the originator product. Japan approved these products only for RA, Crohn’s disease, and ulcerative colitis; meanwhile, the originator has*

ongoing patents in other indications. In contrast, Health Canada initially indicated, that differences (in antibody-dependent cellular cytotoxicity, afucosylation, and FcyRIIIa receptor binding) between the biosimilar and the originator, which could affect clinical safety and efficacy, did not support extrapolation of the clinical data to Crohn's disease or ulcerative colitis without direct clinical assessment. Recently, Health Canada added approvals in Crohn's disease, fistulizing Crohn's disease, and ulcerative colitis based on similarity between the biosimilar and the originator in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen, and on clinical experience with the originator" [129].

The continuously increasing knowledge on cellular mechanisms and signaling pathways in healthy individuals and disease states of patients obtained by utilizing multiple -OMICS technologies in conjunction with the experience gathered by applying mathematical models for data extrapolation, triggered the formation of the EMA „Extrapolation Working Group" (EWG). Members from the scientific committees CHMP, PDCO, SAWP, COMP and methodologists issued a draft reflection paper and concluded the necessity to develop „*a framework for extrapolation approaches that are considered scientifically valid and reliable to support medicine authorization*"[130]. The EWG conceptual approach resulted in the publication of a first draft reflection paper on pediatric indications that „*proposes a framework for extrapolation of data from adults to children which could serve as a basis for regulatory decision making for Pediatric Investigation Plans. Extrapolation for pediatric medicines development is discussed as a model situation but the underlying principles may be extended to other areas of medicine development*" [131].

In fact, the development of treatments for „Orphan Diseases" (ODs) or targeted therapies as part of precision medicine programs would qualify for a corresponding approach. Statistical design and analysis methods for clinical trials were historically developed for confirmatory trials with a high number of study members. As discussed previously in chapter 4.4.2, these methods have not proven successful at acceptable levels to identify treatments for small patient populations, e.g. a defined genetic subgroup, pediatric patients or orphan diseases. Regulatory authorities intended to address the matter. Already in 2007, the EMA „GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS" came into effect providing more flexibility by stating that „*less conventional and/or less commonly seen methodological approaches may be acceptable if they help to improve the interpretability of the study results*" [132]. The corresponding FDA guideline on „Rare Diseases" suggests a „case-by-case approach" on data requirements needed to demonstrate effectiveness and safety of a treatment for any rare disease, but e.g. does not specify a minimum number of patients to be studied [133].

In summary, the limited guidance provided by regulatory authorities resulted in poorly designed studies, statistical challenges and significant deferrals in achieving marketing authorization approval [134], [135]. To overcome the identified deficiencies and to support future research and development programs for the treatment of orphan diseases, the European Commission initiated three multidisciplinary research projects in 2013 as part of the „Research & Innovation"-framework [136]. The initiatives, named „Asterix", „IdeAL" and „InSPiRe", focus on

methodological challenges with regards to design, analysis and interpretation of clinical trials in small populations as observed in clinical trials for orphan diseases and stratified or individualized precision medicine approaches. The development of new methods for extrapolating data from larger clinical trials of similar treatments or the same treatment protocol in different indications or subpopulation might be one solution to provide additional scientific evidence in support of safety and efficacy data obtained from small number clinical trials or even N-of-1 clinical trials.

6.2.2. Regulatory Intelligence (RI)

Precision Medicine research projects are expected to generate a tremendous amount of new data, such as genomic and metabolomic information for diagnostic purposes, new manufacturing processes & controls, analytical methods, surrogate endpoints, biomarkers, patient reporting tools, new disease definitions etc. Furthermore, regulatory authorities are offering novel flexible approval concepts e.g. as part of the EMA „Adaptive Pathways Project“ [137] or the FDA expedited approaches such as „Fast Track“, „Breakthrough Therapy“, „Accelerated Approval“, „Priority Review“ [138] to provide for faster market access of new drugs that may offer substantial benefits over existing treatment options for patients with serious or life-threatening diseases.

As regulatory authorities play a crucial role in the development and market availability of new pharmaceutical products, both agencies recommend considering the potential regulatory impact of new results, scientific publications and guidance documents at an early stage of the research and development plan. The early and continuous dialogue between drug developing companies and regulatory authorities is recommended to avoid delays during the approval process and to focus available resources on potential issues [139].

„Regulatory Intelligence“ comprises the identification and interpretation of such relevant regulatory information. New EMA-, FDA-, WHO-guidelines, „Clinical Trial Applications“ (CTAs) „Annual Reports“ (ARs), the EMA „European Public Assessment Reports“ (EPARs), the FDA „Reviewers Comments“, publications issued by industry associations (e.g. EFPIA, VFA, BPI, BAG, ABPI, LEEM), and „for profit“- (e.g. Cortellis) or „not-for-profit“-organizations (e.g. DGRA) are essential to define the regulatory strategy and interaction with the competent authority for a given development product. Interestingly, RI is not defined identically in the EU and the USA. Whereas the „European Union Regulatory Intelligence Network Group“ (EU RING) defines that „*regulatory intelligence is the act of processing targeted information and data from multiple sources, analyzing the data in its relevant context and generating a meaningful output – e.g. outlining risks and opportunities – to the regulatory strategy. The process is driven by business needs and linked to decisions and actions*“. The „RING“ associated with the US based „Drug Information Association“ (DIA) defines RI as „*the act of gathering and analyzing publicly available regulatory information. This includes communicating the implications of that information, and monitoring the current regulatory environment for opportunities to shape future regulations, guidance, policy, and legislation*“, emphasizing the aspect to influence policy makers [140].

In order to illustrate the various regulatory support and dialogue opportunities to scientists involved in drug developing programs, the „Innovative Medicines Initiative“ (IMI) as part of the European Commission‘s „Seventh Framework Program“ (FP7) and the „European Federation of Pharmaceutical Industries and Associations“ (EFPIA) issued a joint guidance document [141] (Table 9).

	Innovation Task Force (ITF)	Qualification procedure	Scientific advice	Protocol assistance
Scope	Development of emerging therapies and technologies, particularly by SMEs	Novel methodology for specific R&D requirements – may concern several indications or products	Specific to a product (class), and/or indication, and/or pharmaceutical/ manufacturing issue within an R&D program	Product- and indication – specific (rare diseases, EMA designated orphan medicines)
Objective	Receive informal advice and guidance	Receive Advice/Opinion on innovative drug development methods & tools for a specific intended use in the context of R&D in pharmaceuticals, when of regulatory relevance	Receive Advice on the appropriateness of test & studies in development of a medicine (i.e. quality, safety, efficacy questions) – with the aim of marketing authorisation application	Special form of scientific advice, for orphan medicines for rare diseases - with the aim of future marketing authorisation application
Assessment team	N/A ITF briefing meetings are informal and engage a multidisciplinary team of EMA and EU network experts	SAWP/CHMP Qualification Team: QT coordinator, dedicated group of multidisciplinary experts (min 4), incl. expert on 'context of intended use', technical platform, stats), Scientific Officer (EMA)	SAWP/CHMP: Scientific Coordinator, large group of multidisciplinary experts (min 28), Scientific Officer (EMA)	SAWP/CHMP: Scientific Coordinator, large group of multidisciplinary experts (min 28), including COMP members (focus on significant benefit), Scientific Officer (EMA)
Applicants	Any organisation developing innovative medicines or technology, but in particular micro, small and medium-sized enterprises (SMEs)	Consortia, networks, public/private partnerships, learned societies and pharmaceutical industry	Any organisation developing a medicinal product (Pharmaceutical company, academic group, SME, non-EEA SME client company)	Any organisation developing a medicinal product (Pharmaceutical company, academic group, SME, non-EEA SME client company)

Table 9: Overview of interaction opportunities with regulators / EMA on new research projects, depicted from „A Guidance Tool for Researchers“ issued by EFPIA and IMI [141]

In addition, the document outlines the scientific advice provided by EMA and FDA on the qualification of new methodologies and drug development tools generated as part of new projects (see Annex B), options for parallel EMA / FDA scientific advice [142], and EMA / HTA bodies’ parallel scientific advice [143].

The portfolio of pharmaceutical products such as „NCEs“, „Biologics“, „ATMPs“, the corresponding regulatory landscape and the dossier requirements for reimbursements by the statutory health care systems are becoming increasingly comprehensive. Furthermore, the implementation of precision medicine approaches will result in more case by case assessments on the scientific evidence to be provided e.g. to demonstrate a positive benefit-risk-ratio as part of clinical trial applications or marketing authorization filings. Regulatory authorities expect to include and assess the totality of scientific evidence to complement clinical trial data, especially if a small number of patients are enrolled or N-of-1 clinical trials are conducted. Academic research organizations, pharmaceutical companies and contract research organizations (CROs) are challenged to build standardized biorepositories, data management systems and to integrate latest publications and regulatory information to assess the complete scientific evidence available.

The utilization of „Big Data“ analysis tools and „Artificial Intelligence“ concepts might provide one of the solutions to systematically analyze and interpret all relevant regulatory information existing at a certain time point. At the DIA conference, held on June 26-30, 2016 in Philadelphia, PA, USA, speakers representing the pharmaceutical industry, CROs, regulatory authorities and legal consulting firms discussed „*challenges and opportunities in the field of digital data for disease surveillance, personalized medicine and individual stakeholder engagement through innovative tools*“ [144]. A software tool developed as part of the „IBM Watson University Program“ already demonstrates the potential of machine learning platforms. In 2015 a project team from the University of Toronto created „Ross“, an artificial intelligence software supporting lawyers by analyzing all legal resources at its disposal. Based on feedback provided by the users, the system continuously learns and improves the results in return to a specific legal question [145].

Artificial intelligence platforms would be suitable to support regulatory affairs (RA) in multiple ways. Providing RA team members with the latest regulatory intelligence information by automatically scanning the web sites of competent regulatory authorities, RI-platforms and discussion groups, industry- and patients‘- organizations may be complemented by machine learning to answer specific regulatory questions in real time. Moreover, ICH guidelines, meeting reports of regulatory committees, concept- and discussion papers, publically available clinical- and pharmacovigilance-information, drug approval notifications, warning letters and changes to listings of GxP certified companies could be analyzed in order to internally evaluate the benefit-risk-ratio and identify potential deficiencies in data packages intended to be submitted to regulatory authorities. The risk analysis concepts could be even extended to calculate supply chain risks, risk for internal operations and „Environmental Risk Assessment“ (ERA).

6.3. Summary: Ethical Considerations and Regulatory Aspects

The implementation of a precision medicine infrastructure will have consequences for society that will exceed healthcare related aspects in a significant way. The acquisition, storage and analysis of genetic and metabolic data in conjunction with the personal medical history allow identifying the optimal treatment regimen for individual patients based on the current scientific and medical knowledge. However, digital information and biopsies stored in databases and tissue repositories provide the basis for future analysis using new algorithms and technology platforms with unknown potential. Furthermore, the analysis of large data sets on population scale and their correlation with medical records and treatment interventions by “Big Data”- and “Machine Learning” software, will unravel the full potential of the precision medicine approach for public health care systems. Consequently the traditional ethical principles in biomedical research, focusing on the protection of the individual participant in clinical studies, need to be broadened, balancing the interests of society including public healthcare and the accessibility to scientific / medical advancement at affordable costs as well as the individual’s right of data protection towards scientific, social and economic interest groups. Novel regulatory concepts

facilitating precision medicine approaches such as N-of-1 trials in clinical development need to address three major deficiencies observed:

I. The efficient co-development of medicinal products and the corresponding medical devices for detecting their clinical effectiveness requires an integrated process for approval by the competent authorities.
II. Clinical researchers need stringent guidance by the CHMP on standards for the design, analysis and data-interpretation of small-population- and N-of-1 clinical trials
III. Finally, pharmaceutical companies and clinical research institutions need to develop smart data management tools in order to scan and analyze all existing information relevant for a specific development program. The initiation of an early and continuous dialogue with regulatory authorities and HTA bodies will support the timely approval and the demonstration of effectiveness, which in turn will provide the basis for future reimbursement decisions of subscribed medicinal products by the statutory health insurance

7. Conclusions and Outlook:

Personalized diagnostics and therapies will represent the next step for improving therapeutic effectiveness. Supported by significant public initiatives in the EU and USA to establish the necessary clinical and regulatory environment, pharmaceutical companies incorporated this concept into their development programs, as „Statutory Health Insurance“ systems focus their reimbursement budgets on effective treatment options providing significant benefits for individual patients. Consequently, the predominant concept of the past decades to develop and launch „Block-Buster Drugs“ is increasingly replaced by the „Niche-Buster-Concepts“. The latter includes selectively acting chemical and/or biologic active ingredients which may be combined based on profiling data of individual patients obtained by multiple „OMICS“ platform technologies. The individual composition of treatment options with regards to relevant APIs, strengths and pharmaceuticals forms will be associated with decentralized manufacturing and packaging of pharmaceuticals. Decentralized „Micro-Facilities“ or „Specialized Pharmacies“ with e.g. „3-D-Printing“ devices [146], [147] will allow for local manufacture, packaging and e-labelling of individualized therapeutics and are expected to challenge the revenue generating value chain of traditionally operating pharmaceutical companies.

On the other hand, the future development of precision medicine research will have significant consequences for the definition of health and disease, treatment for individual patients including data management and the organization of health care systems. N-of-1 clinical trials designed as prospectively planned multiple crossover trials, conducted in a single individual are a valuable tool, if clinical symptoms are stable or frequently recurring, treatment effects are elicited fast, with limited or no residual carryover effects. Such focused drug development is more selective, expected to be more successful and therefore more ethical to the patient, who has a higher likelihood to be included into a clinical trial improving the individual condition.

As discussed previously, the N-of-1 study design may be a suitable option if the efficacy of a treatment could be measured via short-term endpoints such as biomarkers and metabolites. However, during the last decade regulatory agencies request clinical data demonstrating long-term benefit by assessing long-term endpoints. As a consequence, the trend for long-term efficacy measurements discourages the use of the N-of-1 study design in phase III pivotal trials. The tremendous accumulation of scientific output by applying multiple –OMICS platforms as part of precision medicine approaches and the focus on the identification of meaningful companion diagnostic markers could provide the basis to overcome this limitation. The application of hypothesis-driven „Big Data“ analysis concepts [148] might allow for the establishment of convincing biomarker-phenotype-correlations and risk assessment [149] with N-of-1 studies being one of the trial designs generating valid and predictable data sets to accelerate drug development and to ensure the safety and efficacy of novel treatment options for patients in need.

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Annex A: PerMed Recommendations

All recommendations have been colour-coded according to the activities referred to, which are grouped into three broad areas. However, many recommendations do have a share in two or sometimes all three types of activity (see also figure 3 in chapter 5). In these cases, the recommendation has been assigned to the activity deemed to have the major share.

The colour-coding is as follows:

- Recommendations on biomedical, health-related ICT and health research
- Recommendations on humanities and social sciences research
- Recommendations to improve the framework for implementing PM (e.g. economic, organisational, regulatory, ethical, legal and social)

Challenge 1 – Developing Awareness and Empowerment

1. Provide further evidence for the benefit delivered by PM to health systems.
2. Develop and promote models for individual responsibility, ownership and sharing of personal health data.
3. Develop mobile health applications to maximise engagement of patients with their treatment pathways and track the safety and effectiveness of these interventions.
4. Understand how the changes related to PM will impact public health and ensure they translate directly to benefits for individual citizens and society.
5. Improve communication and education strategies to increase patient health literacy.
6. Incorporate patient participation in the healthcare system and increase the patient's role in all phases of research and development.
7. Develop common principles and legal frameworks that enable sharing of patient-level data for research in a way that is ethical and acceptable to patients and the public.

Challenge 2 – Integrating Big Data and ICT Solutions

8. Promote strategies to make sense of 'big data'.
9. Develop and encourage the fast uptake of technologies for data capture, storage, management and processing.
10. Promote the development of high quality sustainable databases including clinical, health and well-being information.
11. Support translational research infrastructures and enforce data harmonisation fostered by specific ICT infrastructures designed to the health data.
12. Support analytical methods and modelling approaches to develop new disease models, e.g. 'Computerised Twins' or a 'Virtual Patient'.
13. Develop new decision support tools and methodologies of ICT to analyse and interpret data in order to support physicians in their decision-making process.
14. Create a European 'big data' framework and adapt legislation.

Challenge 3 – Translating Basic to Clinical Research and Beyond

15. Develop methods to better integrate and evaluate the information provided by genomic, epigenetic, transcriptomic, proteomic, metabolomic and microbiome analyses.

16. Support research in preclinical models to validate hypotheses resulting from molecular analyses of patient samples and treatment outcomes.

17. Promote collaborative pre-competitive and trans-disciplinary research in all disease areas to gain trustworthy and objective information.

18. Instigate a European-wide biomarker evaluation and validation process.

19. Promote longitudinal studies in the areas of PM.

20. Support developmWent of new clinical trial designs and promote integration with concomitant preclinical testing.

21. Re-classify diseases at the molecular level.

22. Develop suitable funding models to enable cross-sector working in PM research.

Challenge 4 – Bringing Innovation to the Market

23. Formalise a risk-based approach for the evaluation of PM.

24. Optimise individual drug therapies and poly-pharmacy especially in the case of multi-morbidity.

25. Support research on an adequate regulatory and legal framework for PM.

26. Encourage a systematic early dialogue between innovators, patients and decision-makers throughout all regulatory steps to provide guidance and clarity.

27. Facilitate partnerships and innovation networks to encourage cross-disciplinary and cross-border collaboration in research and development using an 'Open Innovation' approach.

28. Provide support and guidance for companies to enter the market for PM with sustainable business cases.

Challenge 5 – Shaping Sustainable Healthcare

29. Support health economics research of PM to support decision makers.

30. Develop prospective surveillance systems for personal health data that facilitate accurate and on-going assessment of highly dynamic health information across the life course.

31. Develop training programmes on PM for health professionals.

32. Encourage a citizen-driven framework for the adoption of electronic health records.

33. Promote engagement and close collaboration between patients, stakeholders and healthcare actors across sciences, sectors and borders.

34. Develop a framework for pricing and reimbursement for PM that ensures equitable access for all patients – regardless of economic or geographic status – and is sustainable for health systems.

35. Develop an optimised overall healthcare financing strategy.

Annex B: Comparison Qualification process (EU) vs DDT process (FDA)

	EMA	FDA
Procedure	3 stages of Qualification Process : • Presubmission • Consultation and advice by the secretariat • Review by the Scientific Advice Working party	3 stages of Qualification Process : • Initiation • Consultation and Advice • Review
Scope	Examples of novel methodologies for which there are formal Qualification programs: • Biomarkers • Preclinical models • Clinical Outcome Assessments • Modelling & statistical methods • Any other novel methodology, e.g. imaging Although scope is not formally restricted	Drug Development Tools for which there are formal Qualification programs: • Biomarkers • Clinical Outcome Assessments (patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes and Performance Outcomes (PerfO)) • Animal Models for use under the FDA Animal Rule
Definition of "qualification" and "context of use"	• **Qualification is a public opinion by** EMA about the specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context. • **Context of use:** specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context. Or in the clinical use of medicinal products.	• **Qualification is a conclusion** that within the stated CoU, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review • **Context of use** describes the way the DDT is to be used and the purpose of the use. A complete context of use should describe fully the circumstances under which the DDT is qualified and the boundaries within which the available data adequately support use of the DDT
Who can apply	**Applicant** = person, group, organisation or consortium; is responsible for the fees and initiates the process	**Submitter** = person, group, organisation (including the federal government), or consortium that takes responsibility for and initiates a DDT qualification proposal using described procedures
When to submit	As early as possible to obtain prospective advice	As early as possible to obtain prospective advice
How to submit/contact	• Initiation request to EMA: contact via email: Qualification • EMA-initiated invitation to submit a Letter of Intent: Electronic submission accompanied by paper cover letter to Central Document Room (see EMA Website for address)	• Initiation request to FDA: contact via email • FDA-initiated invitation to submit a Letter of Intent: Electronic submission accompanied by paper cover letter to Central Document Room (see FDA Website for address) • Contact information for the three Qualification Programs is available on FDA Website *

	EMA	FDA
Documentation	• **Letter of intent-** brief description of drug development tool, intended use of drug development tool (proposed context of use), and brief data overview supporting use of drug development tool in the proposed context of use **For parallel** EMA/FDA **advice:** joint Letter of intent template • Initial Briefing Package- Questions and applicant position: more comprehensive information and discussion describing existing knowledge, known knowledge gaps, and overview of plan to address the gaps. May include detailed statistical analysis plans and protocol outlines • **Full Qualification Package**- A comprehensive submission with complete and detailed description of the studies and analyses providing the evidence to justify qualification of the BM/Method for the intended context of use. Submission of primary data from studies will, in most cases, be expected • **Letter of Support** For those promising biomarkers/methods which are not yet ready for qualification, a Letter of Support may be issued to submitters who have assembled this information about promising biomarkers/methods to encourage further their development.	• **Initiation request-** cover letter with contact information and name of drug development tool **For** parallel EMA/FDA **advice:** joint Letter of intent template • **Letter of intent-** brief description of drug development tool, intended use of drug development tool (proposed context of use), and brief data overview supporting use of drug development tool in the proposed context of use • **Initial** Briefing **Package-** more comprehensive information and discussion describing existing knowledge, known knowledge gaps, and overview of plan to address the gaps. May include detailed statistical analysis plans and protocol outlines • **Subsequent Briefing Packages** to continue consultation and advice as warranted • **Full Qualification Package-** A comprehensive submission with complete and detailed description of the studies and analyses providing the evidence to justify qualification of the DDT for the intended context of use. Submission of primary data from studies will, in most cases, be expected • **Letter of Support** For those promising biomarkers which are not yet ready for qualification, a Letter of Support may be issued to submitters who have assembled this information about promising biomarkers to encourage further their development.
Output of the procedure	Qualification recommendations are issued as official EMA guidance, once an innovative development methods has been qualified for a specific intended use to support a MAA.	Qualification recommendations are issued as official FDA guidance. Once a drug development tool (DDT) has been qualified for a specific context of use in drug development, it can be used to produce analytically valid measurements that can be relied on to have a specific use and interpretable meaning. The DDT can be used by drug developers for the qualified context in IND, NDA and BLA submissions without the relevant CDER review group reconsidering and reconfirming the suitability of the DDT. Drug developers can use qualified DDTs, but are not required to do so.

	EMA	FDA
Confidential/public	• **Initiation, Consultation and Qualification Advice,** Confidential • **Qualification Opinion Recommendation:** at the latest public at MAA and after consultation with the Applicant • **Letter of Support**: Public upon applicant agreement	• **Initiation, Consultation and Advice, and Review Stages:** Confidential • **Qualification Recommendation:** Public • **Executive Summary:** Public • **Redacted Discipline-**Specific Reviews: Public • **Letter of Support:** Public
Fees	Same fee reductions as in scientific advice for paediatric (free), orphan conditions and SMEs (small and medium-sized enterprises (10%)).	None
Length of procedure	Qualification Advice: 100 days Qualification opinion: 190 (dependent upon complexity of submission)	Not defined (dependent upon complexity of submission)
Follow-up	Follow-up Qualification Advice: 100 days Qualification opinion: 190 (dependent upon complexity of submission	Following the Initial Briefing Package submission, additional briefing documents may be submitted to FDA for advice as needed until there is sufficient information available to initiate formal review. Once a qualification recommendation has been made publicly available, the qualification recommendation may be revised as new scientific evidence becomes available

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

(Gunther Kauselmann)

Köln, den 15.06.2017