

**COST Action CA21140: "Interception of oral cancer development"
Medico-economics, ethics and patient's representative Meeting
Minutes**

From 22/09/2023 at 9:00:00 to 22/09/2023 at 17:30:00

Face to face, Lyon, France

Agenda Workshop Interceptor – WP6: Socio-economics, impact and ethics

	TOPIC	WHO
09:00 – 09:15	Welcome	Valesca Retèl
09:15 - 09:45	Introduction Interceptor & clinical perspective to early detection of OPMD	Pierre Saintigny
09:45 - 10:15	Introduction WP6, introduction to HTA & HTA perspective to early detection of OPMD	Valesca Retèl
10:15-10:45	**coffee break**	
11:00 – 11:30	Speaker HTA	Lionel Perrier
11:30 – 12:00	Speaker Policy maker	Wim van Harten
12:00 – 12:30	Speaker Ethical, Legal, Societal Implications	Brenda Bogaert
12:30 - 13:00	Speaker Patient coalition	Antonella Cardone
13:00-14:00	**lunch break**	
14:00-15:30	Roundtable: basis for HTA framework “What are the important determinants to include in the framework from the different stakeholder perspectives?”	All
15MIN	-policy makers	
15MIN	-patient representatives	
15MIN	-HTA	
15MIN	-ELSI	
15:30-16:00	**coffee break**	
16:00-17:00	Interactive:	
	-set up HTA proposal for STSM project on Interceptor (e.g. ISEBIO/ based on RWD hospital data)	Valesca Retèl
	-set up ELSI proposal for STSM project on Interceptor	Brenda Bogaert
17:00	Closure **dinner**	

Management summary

INTERCEPTOR (INTERception of oRal CancEr developMent) Cost Action aims to foster excellent translational research, patient care and education in EU to disease management of oral potentially malignant disorders (OPMD) to prevent the development of oral cancer. We aim to reorganize care and develop a new approach to OPMD care management and propose innovative approaches to prevent oral cancer by leveraging multidisciplinary expertises. At the level of the population, we will study the socio-economic and ethical impacts of developing personalized preventive medicine and work with policy makers and regulation bodies for the implementation of our findings in the population.

The aim of the work package on socio-economic and ethical impact (WP6) is to build a network of Centers having the expertise, facilities and availability and a framework to conduct Health Technology Assessments (HTA) of new preventive strategies for OPMD (such as early detection programs, or biomarkers) for their own country to support implementation and reimbursement.

The aim of the workshop was to construct a basis for a HTA framework concerning early detection for OPMD. In total, twenty-nine participants were present in the hybrid meeting. Four speakers were invited representing four stakeholder perspectives: HTA research, ethical research, policy maker and a patient organization. Subsequently, a roundtable discussion was held concerning the basis for HTA framework “What are the important determinants to include in the framework from the different stakeholder perspectives?”. Finally, potential short-term scientific meetings (STSMs) were discussed and proposed for the coming WP activities.

1. Introduction

The aim of the work package on socio-economics, ethics and impact is to build a network of Centers having the expertise, facilities and availability and a framework to conduct HTA of new preventive strategies for OPMD (such as early detection programs, or biomarkers) for their own country to support implementation and reimbursement.

The aim of the workshop was to construct a basis for a HTA framework concerning early detection of OPMD.

The workshop was introduced by Valesca Retel (WP-leader) with the general goals of the WP, and the goals of the workshop. Subsequently, Pierre Saintigny (COST Action Chair) gave an introductory and clinical perspective of the WP. Four speakers were invited representing four stakeholder perspectives: HTA research, ethical research, policy maker and a patient organization. Subsequently, a roundtable discussion was held concerning the basis for HTA framework, a poll was obtained on the following topic: “What are the important determinants to include in the framework from the different stakeholder perspectives?” Finally, potential STSMs were discussed and proposed for the coming WP activities. In total, twenty-nine participants were present in the hybrid meeting.

2. Clinical perspective

Oral cavity is the most common site of head and neck squamous cell carcinoma (HNSCC) which is ranked as the 8th most common cancer worldwide. Every year, around 350,000 new patients are diagnosed worldwide with oral cavity cancer. OCSCC is the most prevalent oral cavity cancer type. The worldwide mortality rate is 175,000 per year and the 5-year overall survival is about 50%. In Europe (EU), main causes include smoking exposure and to a lesser extent excessive alcohol intake. Around 15% of the patients with OCSCC are non-smokers non-drinkers, mostly young (oral tongue) and elderly (gingiva) women. An increasing incidence of oral mobile tongue SCC has been reported among subjects <45 years old in some countries. In this population, as opposed to human papillomavirus (HPV)-related oropharyngeal SCC, a direct oncogenic role of HPV during carcinogenesis is not established. The role of genetic predisposition factors and environmental factors needs to be better elucidated. [1,2]

Cancer of the oral cavity is not only complex of anatomy, but also in its cause, the exposure is not the same in every country. There could be many commonalities with other cancers, like pancreas, however this is understudied (ranking 16th of cancers worldwide does not help). Only 4% of all oral cancer publications were concerning pre-cancer. [1]

Many different lesions exist under the term OPMD. The prevalence is 4-5% worldwide [1]. In comprehensive cancer centers OPMD often are not seen, they present themselves at the general practitioner (GP), dentist, dermatologist, Ear-Nose-Throat (ENT), Maxillo Facial Surgery (MFS), Oral Medicine in general hospitals.

Standard molecularly based strategies to predict and/or prevent oral cancer development in patients with OPMD are lacking. In a RCT, loss of heterozygosity (LOH) was validated as a marker of oral cancer risk and found to be associated with increased EGFR copy number (the target of the

intervention). This is an example of a biomarker which can select patients for e.g. secondary prevention, this information can be used for comparative analysis, e.g. as a basis for cost-effectiveness analysis.

One of the pillar of EU mission on cancer is to focus on pragmatic trials or activities; prevent what is preventable, develop biologically-driven interventions.

3. Policy perspective

In 2016, a survey was conducted amongst members of the Organization of European Cancer Institutes (OECI), where was found that in 52% of the 29 participating countries, drugs could not be prescribed because of the high costs [4]. Additionally, in 62% of the respondents it was mentioned that treatment choices have financial limitations.

This expression reflects the fact that our healthcare systems in Europe are having financial issues with providing high priced treatments. This causes financial pressure, there is a need for instruments to select the right innovations to be adopted. One of these instruments is HTA, which can help to evaluate the added value of the innovation in terms of clinical, economical, patient-related, organizational and ethical/legal aspects.

Early HTA (eHTA) is increasingly being used to support health economic evidence development during early stages of translational research. EHTA models can be used to inform research and development about the design and management of new medical technologies to mitigate the risks, perceived by industry and the public sector, associated with market access and reimbursement [5]. In early development, the degree of evidence and underlying data on new technologies, organizational approaches, or treatment procedures is limited resulting in levels of uncertainty in which policy advice may be most wanted. Psychosocial and adherence of patients as well as providers, ethical and liability issues, and organizational aspects play a role in the ultimate implementation route. Using various scenarios reflecting different future pathways, the HTA can support the adoption process in guiding development and reimbursement decisions, stepwise reducing the uncertainty as mentioned above [6]. To consider the HTA results, researchers at the institutional level should work with eHTA. It is preferable not to leave HTA to agencies and government.

There are different levels where decisions are made in whether to adopt new technologies and reimbursement. On the macro-level, this is the government, HTA-bodies (such as the National Institute for Health and Care Excellence (NICE)), professional societies, institutional societies, and patient organizations. On the intermediate level there are the regions (e.g. in Italy the regions play a large role in decision making), and health insurance companies. On the institutional level, hospital CEOs are relying on business cases and budget impact analysis for decision making.

The financial structure of healthcare systems are different per country. In the Bismark and Beveridge systems this is different, but also within these systems the funding sources can be different [e.g. by central taxes (UK), regional taxes (Spain), employers' payments and payroll deductions (France, Germany)]. Also, reimbursement schemes are different, Diagnosis-Related Group (DRG)-based, Coverage-with-Evidence-Development programs, using different Willingness to pay thresholds, as well as the type of prices, tariffs and list prices. This means that each country can have a different preference for evidence regarding cost-benefit analyses.

Opportunity costs in terms of equity should be considered in case the budget impact is extremely high, as it will bring the risk of interventions not being reimbursed for other diseases.

According to a publication in the JAMA Internal Medicine, one needs to come with extreme good evidence for policy makers to agree. HTA can help supporting evidence concerning e.g. early cost-effectiveness and budget impact analyses using different scenarios [7,8].

Including Patient reported outcomes (PROMs) and Value Based Healthcare (VBHC) can support HTA-like evidence, utilities can be used in cost-effectiveness analyses to derive Quality-adjusted Life Years (QALYs), and Quality-of-life (QoL) results can be directly discussed by the patient with the physician, to tailor personalized treatment.

4. HTA-research perspective

Prevention and early intervention do not simply tackle the human cost of ill health, they also represent good value for money, reduce demand on public services and support economic growth if implemented in a clinically sound way. However, challenges in the field of prevention are apparent e.g. prevention programs need a certain amount of upfront investment based on highly uncertain outcomes and may lead to overdiagnosis, overtreatment, and waste of resources. Therefore, instruments are needed to understand the socio-economic aspects and consequences of precision preventive medicine. HTA is such an instrument which includes besides clinical effectiveness, also cost-effectiveness, patient-related aspects (e.g. acceptance), and organizational aspects [9].

There is **currently no network of cooperating Centers for HTA in the particular area of prevention of OPMD transformation**. We have to understand the **socio-economic impacts**, as well as the **ethical and sociological implications of the development of a precision preventive medicine of OCSCC** and work together with regulation bodies and policy makers to improve the general population awareness and care givers training.

The socioeconomic impact should be estimated on the long-term: health economics, citizen empowerment, and societal acceptance will play a big role in this analysis. Societal benefits of this INTERCEPTOR Action will focus on improving oral health for citizens of Europe and worldwide. Reducing the malignant transformation of OPMD will lower the incidence of OCSCC, so avoiding expensive treatments impacting on quality of life and patient's functionality.

Regarding the potential cost-effectiveness, several types of prevention strategies including new biomarkers could be modelled in this framework. Prevention of malignant transformation of OPMD should be compared to usual care. Disease stage shift due to prevention programs can be modelled to estimate its benefit. Mainstream cost-effectiveness analyses can be performed in different jurisdictions by means of Markov Models. Agent based models or dynamic simulation models can be used to incorporate behavior, if relevant. Regarding analyses, sensitivity analyses, scenario analyses and return on investment analyses are playing an important role in predicting "future value".

There are some examples in the field of oral cancer and OPMD regarding HTA in terms of economic evaluations and budget impact analyses [10-13]

Another approach could be to estimate the “Population Attributable Fraction” (PAF), using Levin’s formula. Relative risk, population exposed are being included, using e.g. claims data [14].

5. Patient organization perspective

Cancer Patients Europe (CPE) is a European pan-tumor cancer patient organization, with about 50 members from 19 countries. Focus points are policy, research and advocacy. Policy is currently related to the introduction of the EU HTA directive in 2025 [15]. Advocacy concerns priority issues at the EU-level, based on evidence. The CPE is working on a call to action based on a statement focusing on opt-out regarding the European Health Data Space, the regulated opt-out aims at protecting patients’ right to exit research while not jeopardizing the research itself. Furthermore, the CPE is working on the pharmaceutical strategy.

CPE put forward its own position on the definition of unmet medical needs in the pharmaceutical strategy. The definition of “unmet medical needs” cannot be part of a law; innovation is coming faster than the changes that could be made in a law. Definition should not be in a legislation. This definition should not look only at the biology and/or clinical aspects. It should be broader, should include QoL and societal impact.

The implementation of the EU HTA regulation is in process. The text cannot be changed, it is already approved by the EU parliament [16]. The regulation has several ambiguities that should be solved. It has 6 implementing acts, under which the joint clinical assessment. The joint clinical assessment should accelerate access to treatment, try to homogenize systems. There are currently 50 HTA bodies in Europe, each has its own procedures. For each new technology to be available, they have to go through each of the HTA bodies across Europe, and this is after the European Medicines Agency (EMA) approval. All administrative work implies delay in access. Germany is an exception; access is within days after EMA approval. The new European HTA regulation foresees the Joint Clinical Assessment (JCA), implemented at the EU level. What we see as a big problem is that the JCA is not binding for Member States and there is the risk that the joint clinical assessments will be added to the already lengthy process.

CPE advocates for the involvement of patients in the HTA process in a systematic way; not voluntary and in a standardized way across Europe. Good practices are shown in Scotland, Catalonia and France. Examples of patient involvement could be through Simplified Information for patients, such as the HTAi SIP pilot, questionnaires checked and simplified [17]. The inclusion of patient elements i.e. QoL, societal aspects (impact on productivity, impact on family), PROMs are very important and should be standardized as well and should be considered in a prospective study and/or registry including patients with OPMD.

6. Ethical Legal and Social Implications (ELSI) perspective

The development of precision preventive medicine has important sociological and ethical implications. Patient autonomy vs. wellbeing ethical approaches can be discussed in the context of patients with OPMD who are often poorly symptomatic, may never develop cancer and will be asked to give their consent to participate in clinical/biomarker-driven research. In the “care” vs. “cure” ethical approaches, precision preventive medicine will require biospecimens sampling for patient stratification that may lead to the administration of therapies to intercept malignant transformation. Regulation bodies and policy makers will

need to consider the different aspects when discussing reimbursement of tests and treatments, and generalization of screening procedures.

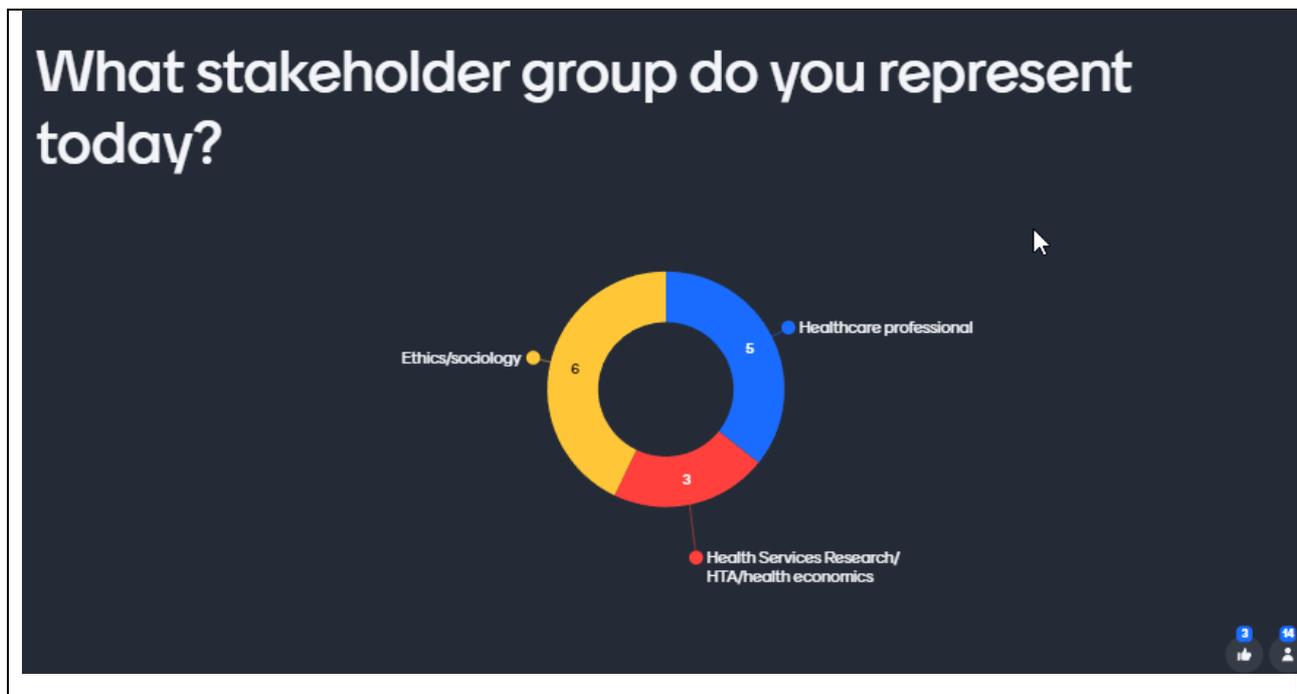
Patients with OPMD transforming or not into OCSCC may have multiple evaluations and interventions by a variety of medical care givers several months up to years before and after the diagnosis of OCSCC. This often involves clinicians with various and heterogeneous training on oral mucosa disorders (general practitioners, smoking-cessation specialists, dermatologists, dentists, ENT surgeons, maxillo-facial surgeons). In fact, patients' healthcare trajectories based on oral disease management is poorly understood thus limiting the global improvement of healthcare monitoring.

From an ethical perspective, there is also the question of fairness and notably who to target for screening, as well as who are the most appropriate stakeholders and how to involve them appropriately in the project. This includes the incorporation of patient representatives, who may bring their experiential knowledge to the project and to policy planning initiatives including patient perspectives of screening. **In the context of our project, better understanding the ELSI perspective should inform ethical and social questions of high-risk screening, how to better involve patients in policy making** (notably with deliberative approaches such as citizen juries), and how to **support patients to both have access to care and better integrate the issues that are important to them in screening and treatment in a person-centered perspective**. This can notably be done with qualitative approaches to gather patient perspectives of OPMD. STSM and a training school are being planned for next year in light of these priorities.

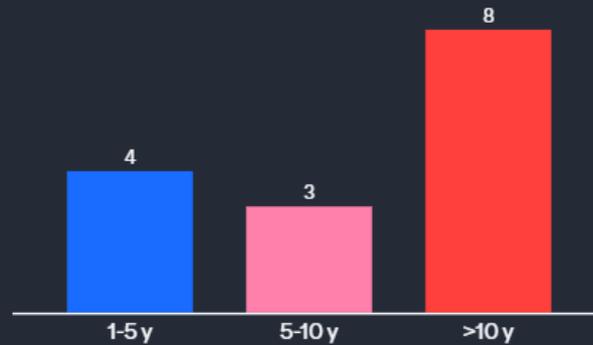
7. Polls with Mentimeter

The meeting in the afternoon was interactive, to find out which topics should be considered in WP6.

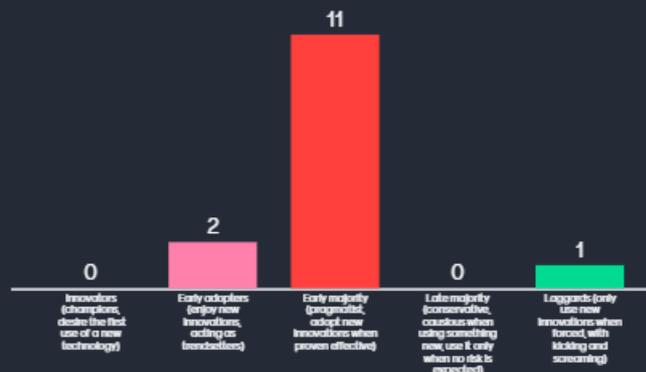
Demographics of the group:



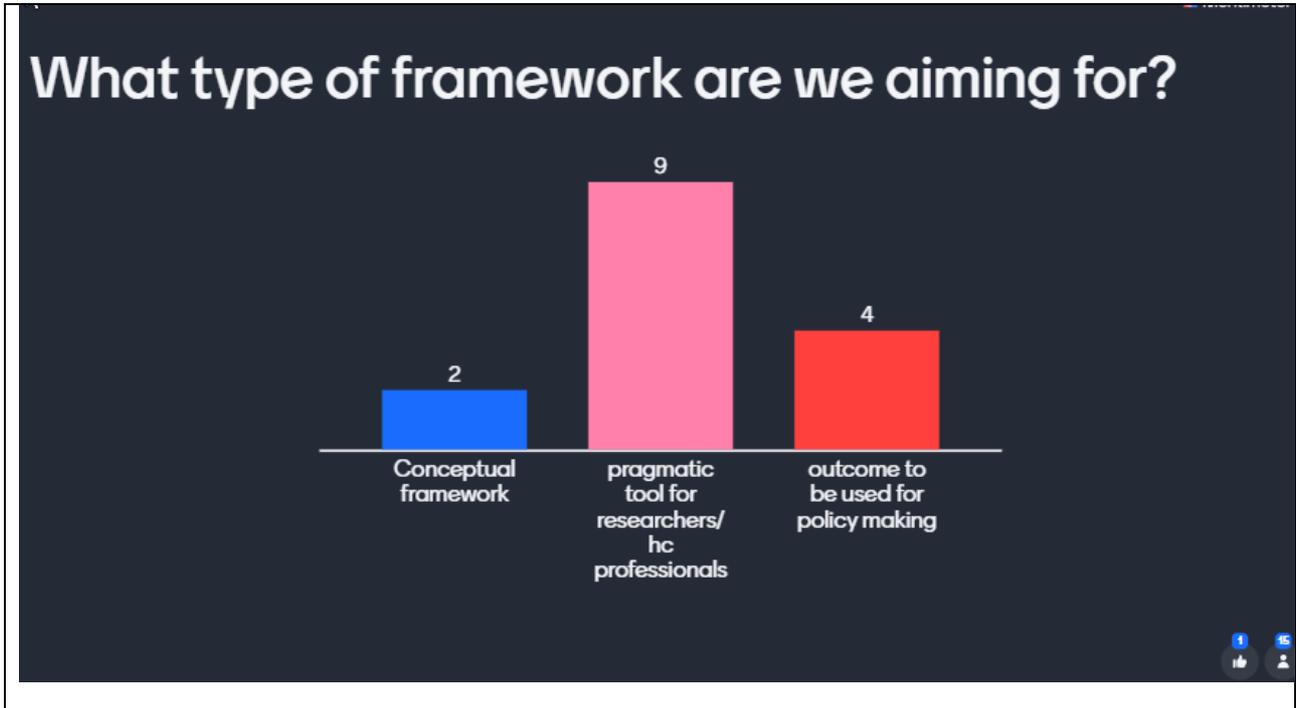
How many years of experience do you have in this field?



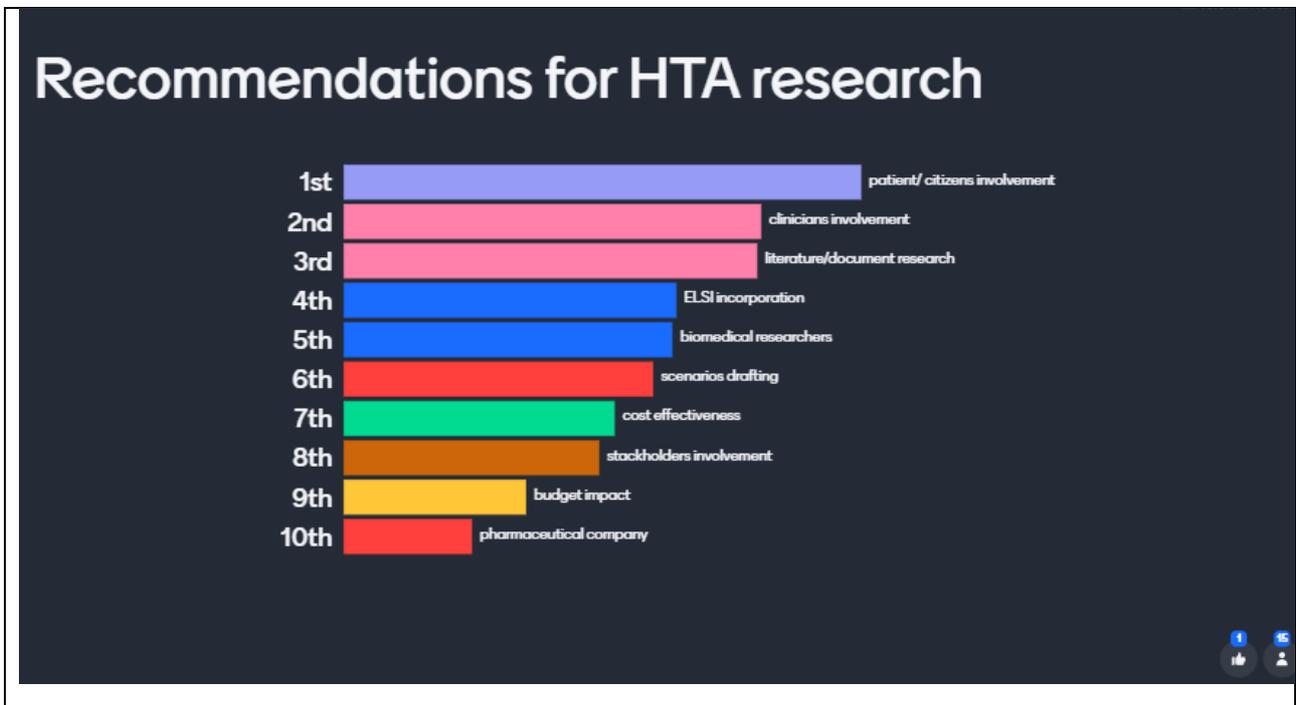
Rogers' adoption curve; which position suits you best?



Question regarding the type of HTA framework we should aim for during the COST Action:



Question regarding what and who to involve in the WP6:



8. Ideas for Short Term Scientific Meetings

Potential STSM topics were formulated in the final session of the day:

1. How patient cope with uncertainty /risk (ethics/ sociology)

-Interview with people (20) who are already detected by OPMD
Currently submitted as a project within the COST Action

2. Deliberation approach with citizens jury and help to develop the methodology

A training school is considered for the COST Action

3. Compare current management in a single institution to *in silico* screening strategy:

Master student for health and cost effectiveness strategy has been appointed (Valesca Retel)
Collaboration with A. Varazzani and P. Saintigny

3. Literature review (Lionel Perrier)

HTA/socio-economic impact and early detection for oral cancer/OPMD

4. Deliberative DCE (Discrete Choice Experiment)

First phase (project) would be to find attributes from a literature review
Second phase (project) would be to perform the DCE with citizens and/or patients

5. Extend the poll from the workshop to the COST INTERCEPTOR network, in particular for policymakers

