IMPORTANT

Horizon Project IMPORTANT

IMPlementing geriatric assessment for dose Optimization of CDK 4/6-inhibitors in older bReasT cAncer patieNTs

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Project Partners

Num.	Partner Name	Short Name	Country
1 (C)	OREBRO LANS LANDSTING	ORB	SE
1.1	Örebro university	ORU	SE
2	PANEPISTIMI PATRON	UPAT	GR
3	UNIVERSITA DEGLI STUDI DI FIRENZE	UNIFI	IT
3.1	AZIENDA OSPIDALIERO-UNIVERSITARIA CAREGGI	AOUC	IT
4	AZIENDA UNITA SANITARIA LOCALE TOSCANA CENTRO	LHUTC	IT
5	HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRIN	HUS	FI
6	INSTITUTE FOR MEDICAL TECHNOLOGY ASSESSMENT BV	IMTA	NL
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12	REGION UPPSALA	RUL	SE
13	FUNDACIO CLINIC PER A LA RECERCA BIOMEDICA	FCRB	ES
13.1	HOSPITAL CLINIC DE BARCELONA	HCB	ES
14	Phaze Clinical Research & Pharma Consulting S.A.	PHAZE	EL
15	BROSTCANCERFORBUNDET	BCF	SE
16	EUNOMIA LIMITED	EUNL	IE
17	FACHHOCHSCHULE NORDWESTSCHWEIZ	FHNW	CH
18	CARE ACROSS LTD	CARE	UK

Project Coordinator: Dr Antonios Valachis - Örebro Läns Landsting (ORB)

List of Authors

Name(s)	Partner
Antonis Valachis	ORB
Mukhrizah Othman	ORB

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Revision History

Date	Ver.	Author(s)	Summary of main changes
30.10.2024	1.1	Mukhrizah Othman	Initial version
30.10.2024	2.0	Antonios Valachis	Final version approved

- **Introduction**

The annual cluster meeting took place on the 12 Sept. 2024 at Vall d'Hebron, Barcelona, Spain. 45 participants representing the 12 funded projects attended physically to the meeting and Marianne Da Silva (HADEA). Additional participants joined remotely. The meeting was chaired by Stephane Lejeune (DE-ESCALATE, EORTC).

The meeting aimed:

  - To present the progress of the 12 funded projects composing the cluster.
  - To discuss cross projects collaboration.
  - To generate material for the two 1st year deliverables "Conclusions of the annual meeting" and "Policy brief".

The agenda is available in annex. The slides and the recordings of the meeting are available from the cluster SharePoint managed by the Prime-Rose project. Access should be requested to Tanja Juslin from the Prime-Rose project

- **Key points of discussion**

- In her introduction, Marianne da Silva (HADEA) presented the EU Mission on Cancer program and answered questions regarding the cluster common deliverables.
  - Currently within the Cancer Mission about 50 funded projects are running within 8 clusters including the diagnostics and treatment cluster. Webinars will be organised across clusters to foster collaboration.
  - Cluster projects are expected to collaborate only on targeted aspects with added value and without disproportionated investment. Cluster projects should not invest resources in cluster activities beyond what is needed for the individual project. The cluster itself is not receiving any specific funding.
  - Responsibilities and timing for preparation of the common deliverables were clarified. The common deliverables are meant to be policy feedback for EU Commission regarding the issues projects are facing. Those deliverables will not be reviewed by HADEA or by external experts but only by DG RTD.
  - Five project officers at HADEA are assigned projects from that cluster. There are discrepancies in the number of common deliverables associated with the cluster meetings. It is recommended to prepare one single deliverable covering 1) the report on the annual meeting (this document) incl. chapters on citizens engagement and inequalities and 2) the policy brief on research and innovation. All cluster projects should submit the same document. Projects with grant agreement requesting two distinct deliverables related to the cluster meeting would be authorized to upload the same document twice.
  - Consortia are asked to invite their patient representative to register as expert on the EU portal to support future EU cancer activities.
  - The responsible project for the organization of the next annual cluster meeting should be identified. Post meeting note: CARE1 proposes to organize the 2nd cluster meeting October 16th 2025 in Berlin, day before ESMO.
- Delegates of the 12 projects presented with update about project progresses.
  - The projects clinical trials are at different development stages, some are progressing according to plan and have already started patient recruitment while others are not yet running and are facing challenges to get the needed regulatory approvals.

- It was agreed that it would be important to allow more time for discussions around specific aspects of the projects to exchange practical experiences and good practice, to address scientific aspects relevant to several projects, etc.. The 2nd cluster meeting should allow sufficient time for it.

- Katriina Jalkanen (PRIME-ROSE, Hus) presented the status of the common deliverable data management plan (DMP).
  - It is not expected that cluster projects will share clinical data but rather that they explore commonalities, exchange of experience and SOPs. We could discuss the preparation of a white paper addressing good practices in data management.
  - The common chapter is ready to be added by cluster projects in their respective DMP deliverable. This was already done by several projects which submitted their DMP deliverable. One project got its DMP deliverable rejected because it used a modified version of the text of the common chapter.
  - As already stated, cluster projects should not go beyond what is expected by EU. However, cluster projects are free to exchange regarding common challenges outside the formal deliverables. Such information could be shared with DG RTD via the policy brief section of the cluster meeting report.

- Susannah Carroll (SALVOVAR) reported on the status of the common deliverable 2: Common video for the "diagnosis and treatment" cluster.
  - A common video was created and is available online. A webpage is also available with the cluster video and specific cluster project videos. A YouTube channel is available.
  - We could establish a LinkedIn account for the cluster. It is to the cluster to decide how to use such communication tools as a group including the possibility to share contacts e.g. subscribers of project newsletter, media, etc. but in compliance with GDPR.
  - Individual projects are free to design their branding and own communication actions in accordance with their grant agreement.
  - One possibility for a cluster communication could be a joint communication around how to involve patient across the cluster projects.

- Frederica Campacci (IMPACT-AML) presented common deliverable 3: Common work plan.
  - The deliverable was finalized in January 2024. This document outlines the collaboration structure in five working groups and the responsibilities of the individual projects in the organisation of events and/or in the related deliverables. Of note, such responsibilities are not described in the grant agreements.
  - This framework can be updated as needed e.g. after every annual cluster meeting. The responsibility for joint deliverables and working groups in the different years is compiled, updated and monitored in the shared file on SharePoint (EU Cluster for Diagnosis and Treatment - responsible projects).
  - There seems to be some discrepancies between the different version of the table identifying responsibilities for cluster deliverables. Cluster projects should share the work in a coordinated manner.

- Denis Lacombe (EORTC) introduced and moderated the debate “What is a pragmatic trial. How does it fit with HTA, payers and regulators’ needs for evidence?”. The current challenges regarding regulatory approval of pragmatic trial and especially treatment optimisation were discussed.

- The implementation of the Clinical Trial Regulation (CTR) is problematic in several aspects including the deployment of the submission and communication platform (CTIS) but also in the way regulators are assessing new clinical trials. Many stakeholders including pharma reported longer timelines before approval but also unrealistic timeline for answering to regulators' queries, numerous and contradictory requests for protocol modifications, etc. The CTR is far from being an efficient process for approving new clinical trials.
- The CTR follows a one fits all approach which is not relevant for many academics led clinical trials. The definition of low interventional trial in the CTR and the impact of such status are questionable. It turns out that the CTR is purposed for the investigation of new drugs with unknown efficacy and safety profiles and not for research involving standard of care involving well known treatments.
- There are also inconsistencies at the EU level between the goals of the EU to improve the wellbeing of its citizens and the way the European regulatory landscape is designed. Regulators have difficulties in approving pragmatic trials especially with a treatment optimisation intent. Regulators are not comfortable with simplified real-life study conduct without strict study monitoring and other control.
- It is striking to observe that EU regulation is preventing the conduct of clinical trial that is EU funded and recognized as valuable for science and society. In the case of the DE-ESCALATE study, already 200,000 euros EU grant were spent without obtaining regulatory approval for starting the study. There is a risk that this public money will be wasted if regulators refuse to approve the study without requesting changes incompatible with the concept of pragmatic trial.
- Furthermore, it looks like regulators are not trusting anymore clinicians as key opinion leaders from the field and are imposing their vision of how a research question should be designed. There is a pragmatic gap between regulatory science (how regulators assess proposed clinical studies), clinical science (how clinicians design research) and ultimately the access science (access for patient to better treatment).
- Academia needs also to be convinced about the value of pragmatic trial investigating the best way of using standard of care when sometime researching new drug clinical trial is more appealing for investigators. There is also the challenge of the attractivity of academic led studies with limited resources when there is competition with pharma clinical trials offering higher compensation to clinical sites. There is sometimes as well the problem of drugs availability in the different EU countries.
- The environment should not be made more complex for clinical research including for pharma companies. While early phase trials are still widely happening, we see that the number of large phase 3 clinical trials is decreasing in Europe. That situation is not only due to a loss of attractivity of Europe but there is also change alongside the progress of science in the direction of smaller precision oriented clinical trials. The problem is also at the level of the member states with treatment reimbursement which is heterogeneous and complex for pharma to cope with.
- We should keep Europe on the map of clinical research. The difficulties come also from the fact that health is a competence of member states, and the EU/EMA has not much decision power. Any discussion for changing the situation e.g. amending the CTR will be therefore complex and lengthy.
- How could we improve the regulatory acceptance of pragmatic trials?

- We should be problem solving. We could suggest to EMA to prepare an official guidance recommending to regulators to show flexibility when assessing pragmatic trial involving well know therapies. In addition, it would be important to train regulators in the assessment of pragmatic trial.
- We need to inform EU that public money is being wasted because of the regulatory gap. HADEA is an implementation agency and DG RTD should be the recipient of such information.
- It would be also important to reach out the member states level. National governments have power and need to contribute improving the situation. DG RTD proposed to share the cluster position paper with the EU Cancer Mission Board.
- We could convey our observations to member states health authorities via the Clinical Trials Coordination Group and the ACT EU initiative involving member states, the EU/EMA, academia, patients and pharma.
- We should act as project cluster and prepare a position paper. The policy brief is the perfect opportunity but must be approved by every cluster member. In parallel, we could write an editorial in a visible scientific journal outside the formal frame of cluster activities.

- Carina Dantas (LIVERATION, SHINE 2Europe) presented WG4 Citizen engagement.
  - Every project should identify one representative to compose a dedicated working group and communicate the contact details to Carina.
  - According to the survey, the understanding of the citizen engagement in research varies across projects. However, for most of the projects, it targets patient. It could also include dissemination and awareness to the public. Most of the projects include patient representative(s). Active engagement from citizens represents a challenge for most of the projects often because of perceived lack of interest. It would be important to go deeper in the different approaches for engaging and communicating with citizens. More information on the survey results is available in the annexes of this report.
  - We will need to prepare the cluster common deliverable Citizen engagement summary report. The content of the deliverable could include how this topic is being addressed in the different projects. It also includes the perspective from the EU: what are the challenges and solutions, best practices for citizen engagement.
  - Joint activities cross cluster projects towards stakeholders' engagement such decision makers could also be considered. Project should provide with information about their activities and events for inventory in the common deliverable. All cluster projects should share relevant information with the LIVERATION team.
  - The progress with this working group should be discussed at every annual cluster meeting and summarized in the related report. The deliverable should include a summary of all what was done concretely and discussed during annual cluster meetings.
- Susannah Carroll (SALVOVAR, HCL) presented the progress of WG2 – Dissemination and Communication of the Results.
  - It was confirmed that EU expectations regarding common deliverable for communication and dissemination are fulfilled with the common video and website.

- What could we communicate together as a cluster closer to the end of the projects? We could communicate about the results of the clinical trials and about the lessons learned. Such communication should be tailored depending on the targeted audience: clinicians, patient, decision makers, etc. We should reach not only the cluster community but also the rest of the stakeholders.
- It is difficult to foresee which messages would be relevant in several years from now. We should continue to brainstorm about that and how to communicate it along the life of the cluster.

- Laurence Albiges (CARE1, IGR) introduced WG3 Research and innovation.
  - It is expected from cluster members to identify new issues and development regarding pragmatic trials in Europe and to share such information with stakeholders. We could prepare a white paper on methodology and best practices but also about the challenges faced by the cluster projects and what are the solutions proposed to EU to make future research easier.
  - Specific innovation topics could include ePRO and automated data extraction via eCRF that are relevant topics for pragmatic trials. The general question could be “how to make digital tool pragmatic and the measured outcomes meaningful for patients?”.
  - We should also discuss with patient representatives what means innovation? We could also investigate how patients find the information regarding to disease and treatment. How could we make patient information access fair and universal thanks to technology & innovation?
  - CARE1 will survey the cluster projects investigating which innovation is involved in their respective clinical trial. This will provide with material for the next round of discussions.
- Katriina Jalkanen (PRIME-ROSE, Hus) presented WG1 – Collaborative framework and Data Management.
  - The common chapter should be included in the DMP deliverable as it is without modification otherwise it will be rejected by EU.
  - It is not foreseen to share or combine cluster projects clinical data, but we could address commonalities and common challenges in collecting and analyzing clinical data and managing clinical research projects in full compliance with GDPR and other applicable regulations. It could be useful to share the lessons learned to not do the same mistake than other projects
  - It is proposed to discuss the feasibility of the standardization of common data variables between projects using OMOP. Could we design common research questions and then interrogate the databases of the cluster projects and share the results? Such federated and distant learning approach would request significant efforts and resources that are not foreseen in projects’ budget.
- Antonios Valachis (IMPORTANT, Orebro Univ) reported the progress of the WG5 - Addressing inequalities.
  - A questionnaire was circulated to collect observations regarding the occurrence of inequalities and social disparities in the different projects and how to address them. Answers were received from six projects. Similar inequalities and disparities were reported: including access to drug, to care, barriers to participation to clinical trial e.g. for elderly, etc. Some mitigation strategies were reported. Preliminary results identify three

main groups of inequalities across Europe: (1) reimbursement strategies; access to medication (or laboratory procedures); (2) participation to clinical trial; and (3) heterogenous healthcare resources.

- A few other aspects were raised by other projects during the round table discussion:
  - Gender domain should be defined and included into addressing inequalities aspect of cluster work.
  - It is difficult to find patients reported experience measures that are validated. Some projects under the cluster are collecting patients' experience, and this could be a good source for evaluating inequalities. It is good to identify what tools are used for evaluating patients' experience by those projects.
  - How can we ensure all eligible patients are included in the trial? This could be related to practices by hospital management e.g. in providing access to molecular screening to see if patients are eligible for a targeted therapy trial.
  - There are 12 projects under the cluster with some redundant countries. We can see if there is a pattern related to care pathway. It would be good to see if the expected number of patients stated for each country is consistent across the different countries and disease type because patient flow and access to the trial are not the same. Does the number of expected patients matches the basic demographic of the country? Some countries with high population may have less patients due to poor health literacy.
- Next step will be to relaunch the survey to get more replies to enrich the data. Dedicated follow-up meetings will be organized thereafter to discuss the findings and solutions. Progresses will be reported during annual meetings. The conclusion will be presented in the final meeting report.

- Conclusions:
  - It was important to meet face to face since this is fostering interactions and facilitating future collaboration. We have started to brainstorm about common position papers and other activities which could show the added value of the cluster.
  - We received useful clarifications from HADEA regarding reporting duties.
  - S Lejeune drafted the report and other cluster members provided input for their corresponding parts in the report. CARE1 will prepare the policy brief. Presenters uploaded their slides on the cluster SharePoint.
  - Thanks to all participants for their contribution and especially Vall d'Hebron for hosting the meeting.

Annexes

Agenda

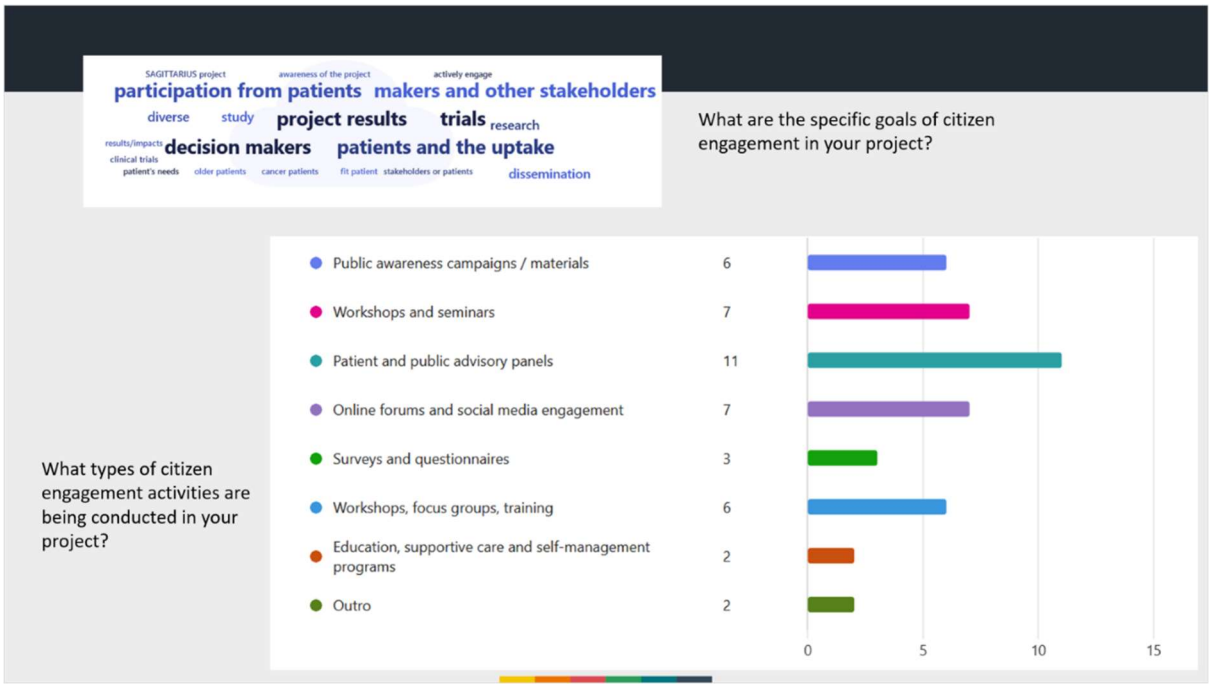
Timing	Topics	Speakers
10h00	**Welcome**	Stephane Lejeune (DE-ESCALATE, EORTC) Alejandro Piris (PragmaTIL, VHIO)
10h05	**Introduction**: What is expected by the EU from the cluster meeting?	Marianne da Silva (European Health and Digital Executive Agency)
10h15	**Status of the 12 projects** (5 min per project) - Project objectives, design and status. - What is expected from the cluster activities and meeting.	Projects representatives
11h15	**Status & timeline common deliverable 1: Data Management Plan** (10 min report & 10 min discussion)	Katriina Jalkanen (PRIME-ROSE, Hus)
11h35	**Coffee break**	
12h00	**Status & timeline common deliverable 2: Communication plan** (10 min report & 10 min discussion)	Susannah Carroll (SALVOVAR,)
12h20	**Status & timeline common deliverable 3: Common work plan** (10 min report & 10 min discussion)	Giovanni Martinelli (IMPACT-AML, IRST)
12h40	**Lunch**	
13h40	**Debate "What is a pragmatic trial. How does it fit with HTA, payers and regulators' needs for evidence?"** **Introduction (20 min)** - Report from the "Cancer Medicines Forum Workshop" (5th April 2024, EMA-EORTC) - Regulatory challenges. The case of De-Escalate. The ACT-EU initiative. **Debate with cluster members (60 min)** - Is the pragmatic trial approach appropriate for answering to your research questions? - Does pragmatic trial fit with HTA, payers and regulators' needs for evidence? - Did you experience challenges in obtaining the regulatory approval? - How could we improve regulatory acceptance? Policy action?	Introduction and moderation: Denis Lacombe (EORTC)

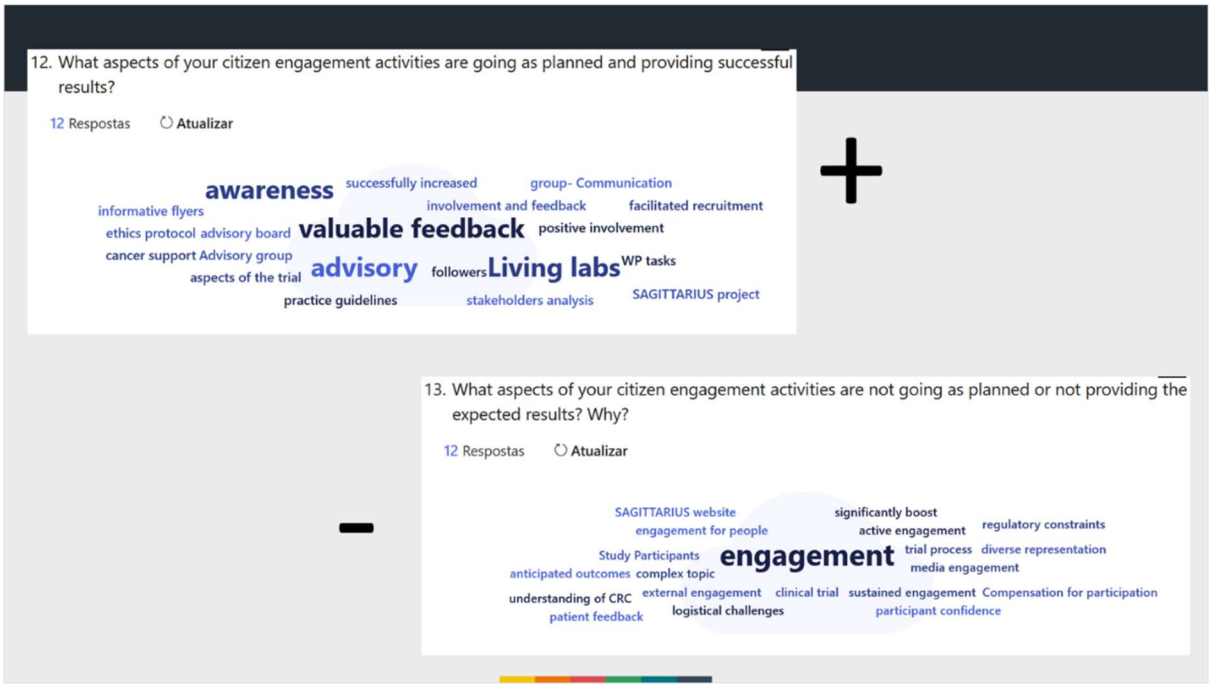
15h00	**Round table: WG4 - Citizen engagement**	Carina Dantas (LIVERATION, SHINE 2Europe)
15h30	**Round table: WG2 – Dissemination and Communication of the Results**	Susannah Carroll (SALVOVAR,)
16h00	**Coffee break**	
16h20	**Round table: WG3 - Research and Innovation**	Laurence Albiges (CARE1, IGR)
16h50	**Round table: WG1 – Collaborative framework and Data Management**	Katriina Jalkanen (PRIME-ROSE, Hus)
17h20	**Round table: WG5 - Addressing inequalities**	Antonios Valachis (IMPORTANT, Orebro Univ)
17h50	**Wrap up/ action list**	Stephane Lejeune (DE-ESCALATE, EORTC)
18h00	**End**	

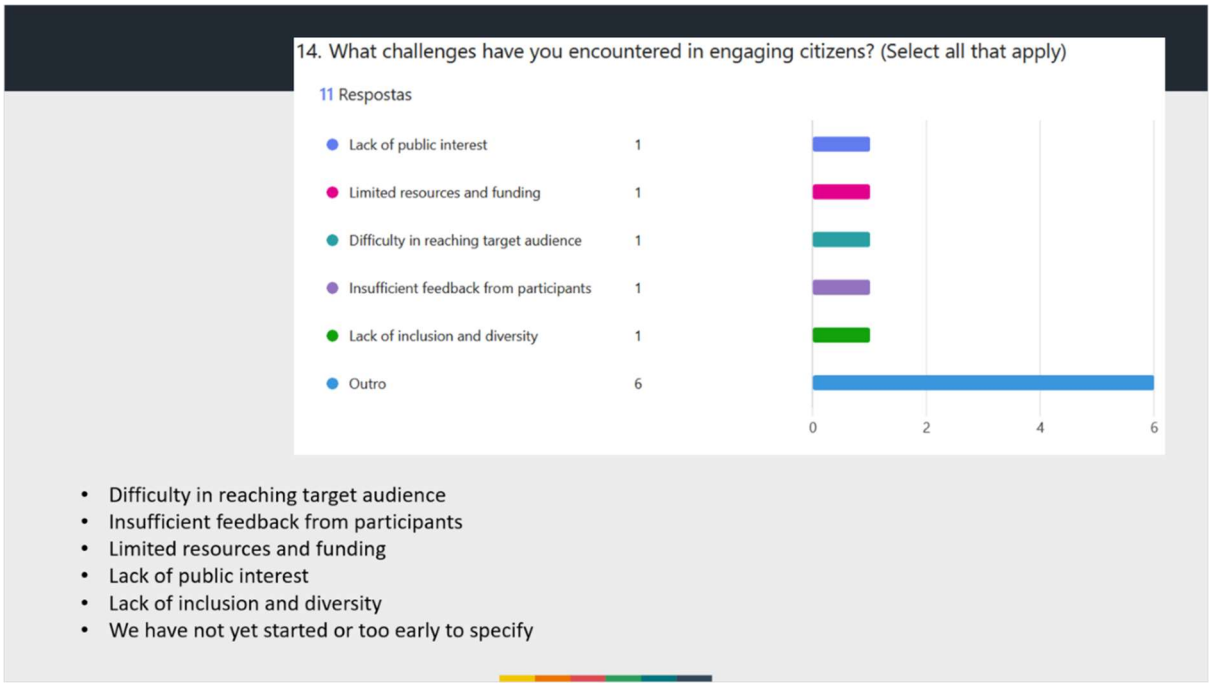
Results from the citizen engagement survey

What does your project consider as Citizen Engagement and how does it differ from e.g. patient or stakeholder engagement?

- Several projects consider mostly PATIENT engagement (incl. caregivers and family members)
- Almost all of the projects include here DISSEMINATION and AWARENESS to the general public
- This include things such as PODCASTS, TRAINING - and more traditional: newsletters, leaflets, social media
- Most of the projects have Patient Boards, Advisory Boards or even a COMMUNITY BOARD
- PPI, CO-RESEARCH, LIVING LABS are some of the innovative approaches taken
- Some of the projects also consider MULTISTAKEHOLDER ENGAGEMENT incl. policy makers, regulators, etc.







What lessons have you learned so far?

- Plan ahead more carefully, annual clock with milestones ready 2 months prior
- Opinions from patient / caregiver advisory panel are valuable and important
- Good public campaign cost a lot, 10 times more than planned, and do not fit very well in 6 million budget. With cost restrictions, initiatives addressing the large public remain poorly applicable

- Adaptative Communication: Providing clear, concise, and tailored information (patient-friendly) that meets the specific needs of our audience. This approach helps in exposing complex topics
- Social Media's Role in Engagement: engagement is highest when content is not only informative but also interactive and relatable. Ex. Healthy Tips has had good engagement from the followers
- Need for Continuous Content Updates: continuous updates and new content are necessary to keep the public engaged and informed, which also helps in building and maintaining trust. We try to post on Social Media one post per week.
- Citizen engagement is a valuable method for gathering insights into the needs and expectations of a broader population. The feedback collected should be carefully considered in shaping the project's development and in adjusting future activities accordingly.
- As a pragmatic clinical trial, we must also adapt most documents concerning patients as to improve their understanding of the trial and its impact.
- Patient organizations and social media are valuable for recruitment, but personal contacts and referrals offer significant advantages.
- Recruitment is time-consuming, and it is important to adapt engagement strategies to evolving circumstances and maintain flexibility in participation
- Providing clear, accessible information and support for complex medical topics is essential, as is addressing language barriers (especially in multinational trials).
- It is important to balance citizen/stakeholder feedback with regulatory and technical constraints, and to communicate these limitations. - Setting clear expectations for participants is also crucial.
- There is a need for improvement in education, information and communication with patients during the clinical trial. A major need on improving supportive care and access and referrals to supportive care strategies and self-management advice also emerged.

What support / resources would help improve your efforts?

- Some projects reported none or not for the moment
- A better designed communication campaign
- Budgets for dissemination and further special meetings
- To improve our citizen engagement efforts, having more interaction with other Cluster Projects and exchange experiences could be beneficial.
- In addition to the methods that support citizen engagement (education and training, incentive, feedback mechanisms), partnering with relevant stakeholders can improve engagement efforts.
- Digital support for creating content for patients

- Knowledge at a European scale of regulation on which data can we communicate to patients and their relatives - to have a regulatory homogeneity on a European scale
- "Support or guidance for dealing with the many hurdles of remuneration (e.g., differing taxation rules, payment systems, regulatory compliance, currency exchange, etc).
- Stronger stakeholder networks – to facilitate connecting with interested individuals (such as patient advocacy groups, community organizations, healthcare professionals) – would broaden recruitment and engagement efforts.
- Shared learning from other projects that have faced similar challenges to share best practices & avoiding common pitfalls in these types of projects. "
- The supportive care resources that we will develop could be developed in collaboration with other trials which could also make use of them.